0031-6997/00/5204-0595$03.00/0
PHARMACOLOGICAL REVIEWS
U.S. Government work not protected by U.S. copyright
Pharmacol Rev 52:595–638, 2000

Vol. 52, No. 4
41/865371
Printed in U.S.A

The Sympathetic Nerve—An Integrative Interface between Two Supersystems: The Brain and the Immune System

ILIA J. ELENKOV, RONALD L. WILDER, GEORGE P. CHROUSOS, AND E. SYLVESTER VIZI[1]

Inflammatory Joint Diseases Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland (I.J.E., R.L.W.); Pediatric Endocrinology Section, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland (I.J.E., G.P.C.); Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary (E.S.V.); and Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary (E.S.V.)

This paper is available online at http://www.pharmrev.org

[1] Address for correspondence: Dr. E. Sylvester Vizi, Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, H-1450 Budapest, P.O. Box 67, Hungary. E-mail: esvizi@koki.hu

Abstract——**The brain and the immune system are the two major adaptive systems of the body. During an immune response the brain and the immune system "talk to each other" and this process is essential for maintaining *homeostasis*. Two major pathway systems are involved in this *cross-talk*: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This overview focuses on the role of SNS in neuroimmune interactions, an area that has received much less attention than the role of HPA axis. Evidence accumulated over the last 20 years suggests that norepinephrine (NE) fulfills the criteria for neurotransmitter/neuromodulator in lymphoid organs. Thus, primary and secondary lymphoid organs receive extensive sympathetic/noradrenergic innervation. Under stimulation, NE is released from the sympathetic nerve terminals in these organs, and the target immune cells express adrenoreceptors. Through stimulation of these receptors, locally released NE, or circulating catecholamines such as epinephrine, affect lymphocyte traffic, circulation, and proliferation, and modulate cytokine production and the functional activity of different lymphoid cells. Although there exists substantial sympathetic innervation in the bone marrow, and particularly in the thymus and mucosal tissues, our knowledge about the effect of the sympathetic neural input on hematopoiesis, thymocyte development, and mucosal immunity is extremely modest. In addition, recent evidence is discussed that NE and epinephrine, through stimulation of the β_2-adrenoreceptor-cAMP-protein kinase A pathway, inhibit the production of type 1/proinflammatory cytokines, such as interleukin (IL-12), tumor necrosis factor-α, and interferon-γ by antigen-presenting cells and T helper (Th) 1 cells, whereas they stimulate the production of type 2/anti-inflammatory cytokines such as IL-10 and transforming growth factor-β. Through this mechanism, systemically, endogenous catecholamines may cause a selective suppression of Th1 responses and cellular immunity, and a Th2 shift toward dominance of humoral immunity. On the other hand, in certain local responses, and under certain conditions, catecholamines may actually boost regional immune responses, through induction of IL-1, tumor necrosis factor-α, and primarily IL-8 production. Thus, the activation of SNS during an immune response might be aimed to localize the inflammatory response, through induction of neutrophil accumulation and stimulation of more specific humoral immune responses, although systemically it may suppress Th1 responses, and, thus protect the organism from the detrimental effects of proinflammatory cytokines and other products of activated macrophages. The above-mentioned immunomodulatory effects of catecholamines and the role of**

SNS are also discussed in the context of their clinical implication in certain infections, major injury and sepsis, autoimmunity, chronic pain and fatigue syndromes, and tumor growth. Finally, the pharmacological manipulation of the sympathetic-immune interface is reviewed with focus on new therapeutic strategies using selective α_2- and β_2-adrenoreceptor agonists and antagonists and inhibitors of phosphodiesterase type IV in the treatment of experimental models of autoimmune diseases, fibromyalgia, and chronic fatigue syndrome.

I. Introduction

A. Overview

The brain and the immune system, or the "supersystems", a term recently coined by Tada (1997), are the two major adaptive systems of the body. Although the immune system has been often regarded as autonomous, the last two to three decades provided strong evidence that the central nervous system (CNS[2]) receives *messages* from the immune system and vice versa messages from the brain modulate immune functions. Thus, the brain and the immune system are involved in functionally relevant *cross-talk*, whose main function is to maintain *homeostasis*.

Two pathways link the brain and the immune system: the autonomic nervous system (ANS) via direct neural influences, and the neuroendocrine humoral outflow via the pituitary. The general immunosuppressive and anti-inflammatory effects of adrenal glucocorticoids, the end-products of the hypothalamic-pituitary-adrenal (HPA) axis, have been known for over 50 years. Evidence accumulated over the last two decades indicates, however, that the sympathetic nervous system (SNS), a major component of the ANS, innervates all lymphoid organs and that catecholamines (CAs), the end products of SNS, modulate several immune parameters. Thus, primary and secondary lymphoid organs are not only extensively *hardwired* by noradrenergic nerve terminals but also the immune cells, thereby the immune system is *tuned* by norepinephrine (NE) released locally from nonsynaptic varicosities or circulating epinephrine secreted by the adrenal medulla. Therefore, the SNS provides another major integrative and regulatory pathway between the brain and the immune system.

CAs, similar to glucocorticoids, have been often regarded as immunosuppressive. Recently, however, there has been accumulating evidence that both CAs and glucocorticoids, under physiologic conditions or at levels that can be achieved during stress, influence the immune response in a less *monochromatic way*. This new understanding helps explain some well known, but often contradictory, effects of the neuroendocrine or stress system on the immunity and on the onset and course of common human pathologic conditions, such as infections, autoimmune/inflammatory, allergic, and neoplastic diseases.

In the present overview, we shall attempt to provide a summary of this evidence and to review current concepts and ideas of how the SNS and the immune system influence each other, with a focus on the roles of the main sympathetic neurotransmitter NE and the main sympathoadrenal hormone epinephrine at the sympathetic-immune interface. Emphasis has been placed on physiological, functional, and pharmacological aspects of the SNS-immune communication.

B. Historical Perspectives

Neuroscience and immunology developed independently for many years. Thus, the question how the brain communicates with the immune system remained enigmatic until comparatively recently. Evidence that lymphoid organs are innervated dates back to the end of last century when nerves, independent of blood vessels, were found to enter lymph nodes (Tonkoff, 1899). Between 1880 and 1920, J. N. Langley, in conjunction with H. K. Anderson, defined the major functional features of the sympathetic and parasympathetic systems, showing how different effector tissues were affected by segmental ventral root stimulation (cf. Janig and McLachlan, 1992a). In 1898, Otto von Fürth

[2] Abbreviations: CNS, central nervous system; Ab, antibody; AC, adenylate cyclase; AP-1, activator protein 1; APC, antigen-presenting cell; ANS, autonomic nervous system; AR(s), adrenoreceptor(s); ACTH, adrenocorticotropic hormone; ATD, autoimmune thyroid disease; βARK, β-adrenergic receptor kinase; BALT, bronchus-associated lymphoid tissue; BDNF, brain-derived neurotrophic factor; BCDF, B cell differentiation factor; BSA, bovine serum albumin; CaM, calmodulin; CaN, calcineurin; CAs, catecholamines; CD, cluster of differentiation; CFS, chronic fatigue syndrome; CGRP, calcitonin gene-related peptide; CRE, cAMP-responsive element; CREB, CRE-binding protein; CFU, colony forming units; CRH, corticotropin-releasing hormone; DA, dopamine; DAG, diacylglycerol; DBH; dopamine β-hydroxylase; DOPA, dihydroxyphenylalanine; EAE, experimental allergic encephalomyelitis; GALT, gut-associated lymphoid tissue; GRK, G-protein-coupled receptor kinase; GM-CFU; granulocyte-macrophage colony forming units; HPA; hypothalamopituitary-adrenal axis; IFN, interferon; IL, interleukin; JRA, juvenile rheumatoid arthritis; LC, locus ceruleus; LEW, Lewis rats; LPS, lipopolysaccharide; MCP, monocyte chemotactic protein; ME, median eminence; MIP, macrophage inflammatory protein; MS, multiple sclerosis; NE, norepinephrine; NK, natural killer cell; NO, nitric oxide; NT3, neurotrophin 3; NGF, nerve growth factor; NPY, neuropeptide Y; NF-AT, nuclear factor of activated T cell; NF-κB, nuclear transcription factor κB; 6-OHDA, 6-hydroxydopamine; PAF, platelet-activating factor; PBMC, peripheral blood mononuclear cells; PDE, phosphodiesterase; PGE, prostaglandin E; PI, phosphatidylinositol; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PVN, paraventricular nucleus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SRBC, sheep red blood cell; SNS, sympathetic nervous system; SP, substance P; Tc, T cytotoxic lymphocyte; Th, T helper lymphocyte; Ts, T suppressor lymphocyte; TCR, T cell receptor; TEC, thymic epithelial cell; TGF, transforming growth factor; TH, tyrosine hydroxylase; TNF, tumor necrosis factor; TNP, trinitrophenyl; VIP, vasoactive intestinal peptide.

isolated a bioactive compound from animal tissue and called this partly purified product "Suprarenin". Three years later, Takamine and Aldrich independently isolated the responsible component in crystalline form (cf. Benschop et al., 1996). Takamine named the substance, and Aldrich found the correct formula ($C_9H_{13}NO_3$). Thus, about 100 years ago adrenaline (epinephrine) was the first hormone to be isolated from tissue. During experiments in 1907, a by-product in the synthesis of adrenaline was identified. This substance, which became commercially available as "Arterenol" in 1908, was in fact noradrenaline (norepinephrine), which would formally be discovered and isolated from tissue 40 years later. Since the effects of Arterenol were less pronounced than those achieved by adrenaline, production was cancelled in 1910 (cf. Benschop et al., 1996).

At the end of the last century and at the beginning of this century Ilya Metchnicoff and Paul Ehrlich, respectively, developed the concepts of cellular and humoral immunity (see Paul, 1993), while Sherrington introduced the concept of chemical neurotransmission (cf. Vizi and Labos, 1991). Loeper and Crouzon (1904) were the first to describe a pronounced leukocytosis after subcutaneous injection of the adrenomedullary hormone epinephrine in humans. Ishigami (1919) was probably the first to indicate the role of the stress-immune system interaction in alteration of the infectious process. In 1919, studying subjects suffering from chronic tuberculosis, he observed a decrease in the phagocytic activity of leukocytes during the periods of greatest psychological stress. In the 1920s Metal'nikov and Chorine (1926) showed that immune reactions could be conditioned by classical Pavlovian means. Later, anatomists used silver staining to demonstrate that the thymus gland is innervated (see Kendall and Al-Shawaf, 1991). However, at this time, the thymus was regarded as a rudimentary organ, whose function as a primary lymphoid organ of the immune system would be discovered only 30 years later. In the 1930s, Hans Selye described involution of the thymus in animals exposed to stressors and developed the concept of stress response (Selye, 1936). Also in the 1930s, physiologists like Walter Cannon called this response "fight or flight" reaction and linked the adaptive response to stress with CA secretion and actions. Cannon also emphasized the "generalized" sympathetic response, or the "wisdom of the body" that occurs during stress, contrasting this with more "discrete" functions of parasympathetic pathways (see Chrousos and Gold, 1992; Janig and McLachlan, 1992a). At about the same time, pharmacologists like Loewi and Dale, in pursuing the concept of chemical synaptic transmission, mimicked the responses of peripheral organs to autonomic nerve stimulation by applying substances that they could extract from the same or other peripheral organs.

In the 1940s, von Euler (1946) isolated from a lymphoid organ, the spleen, norepinephrine (NE) and later provided evidence that NE is the major neurotransmitter released from sympathetic nerves. However, in the next two decades the spleen was often considered as a "blood reservoir", and studies concerning the role of sympathetic innervation of the spleen focused on its role in regulation of splenic contraction (of the capsule, in rodents and certain mammals), vascular resistance, and blood flow. This led to the assumption, at this time, that NE-containing nerve fibers in the spleen have no other functions. Interestingly, in the 1950s, Dougherty and Frank (1953) noticed about a 400% increase within 10 min after subcutaneous injection of epinephrine of what they called "stress-lymphocytes". These cells had the morphology of large granular lymphocytes or natural killer (NK) cells, whose function and characteristics were described in the late seventies (see Benschop et al., 1996).

Only in the 1970s and the 1980s, however, due to the pioneering work of Hugo Besedovsky and coworkers, did it become clear that classic hormones and newly described cytokines are involved in functionally relevant *cross-talk* between the brain and the immune system (Besedovsky et al., 1975, 1979, 1986). They have shown that an immune response induces an increase of plasma corticosteroid levels (Besedovsky et al., 1975, 1981, 1986), alters the activity of hypothalamic noradrenergic neurons (Besedovsky et al., 1983), and drops the content of NE in the spleen (Besedovsky et al., 1979; Del Rey et al., 1982). Also in the 1970s, the first hormone receptor on lymphocytes was described functionally, when it was reported that adrenergic agents modulate lymphocyte proliferation (Hadden et al., 1970). In the 1970s and 1980s, the first comprehensive morphological studies provided evidence that both primary and secondary lymphoid organs are innervated by sympathetic/noradrenergic nerve fibers (see text below). Furthermore, altered immune function has been induced by classical behavioral conditioning (Ader and Cohen, 1982), by stressful stimuli (Keller et al., 1983; Cohen et al., 1991; Chrousos, 1995), or by lesions in specific regions of the brain (Carlson and Felten, 1989b). Finally, evidence was obtained in experimental animals that the susceptibility to autoimmune diseases is modulated by the activity of the stress system (Sternberg et al., 1989a,b; Wilder, 1995) or that stress mediators may exert both pro- and anti-inflammatory effects (Karalis et al., 1991; Chrousos, 1995). Thus, in the last two decades we witnessed an explosive growth of a new interdisciplinary research area that studies the neuroimmune communication, or simply, the physiology and pharmacology of the immune system.

II. Anatomy and Physiology of the Autonomic Nervous System

A. Organization of the Autonomic / Sympathetic Nervous System

The ANS regulates the function of all innervated tissues and organs throughout the vertebrate body with the exception of skeletal muscle fibers. Thus, it forms the major efferent component of the peripheral nervous system,

containing integrative neuronal connections and even complete reflex arcs. The ANS is largely autonomous (independent) in that its activities are not under direct conscious control. The ANS consists of three components: the sympathetic (noradrenergic) and parasympathetic (cholinergic) systems, which originate in the CNS (with cell bodies in the brainstem and spinal cord); and the enteric system, which lies within the wall of the gastrointestinal tract. The most extensive and physiologically most diverse component is the SNS, which sends axons to all parts of the body. The enteric system, which contains a similar number of neurons as the spinal cord (Furness and Costa, 1980), regulates intestinal functions; this system is modulated by projections from the sympathetic and the parasympathetic systems (Vizi et al., 1991).

The sympathetic division originates in nuclei within the brain stem and gives rise to preganglionic efferent fibers that leave the CNS through the thoracic and lumbar spinal nerves ("thoracolumbar system"). Most of the sympathetic preganglionic fibers terminate in ganglia located in the paravertebral chains that lie on either side of the spinal column. The remaining sympathetic ganglia are located in prevertebral ganglia, which lie in front of the vertebrae. From these ganglia, postganglionic sympathetic fibers run to the tissues innervated. Most postganglionic sympathetic fibers release NE; they are noradrenergic fibers; i.e., they act by releasing NE. The adrenal medulla contains chromaffin cells, embryologically and anatomically homologous to the sympathetic ganglia in that they are derived from the neural crest. The adrenal medulla, unlike the postganglionic sympathetic nerve terminals, releases mainly epinephrine, and to a lesser extent NE (the approximate ratio is 4:1); the chromaffin cells of the adrenal medulla are innervated by typical preganglionic sympathetic nerve terminals, whose neurotransmitter is acetylcholine. Thus, the principal end products of the SNS are NE and epinephrine, called CAs (Fig. 1).

CAs are synthesized from tyrosine that is transported into the noradrenergic ending or varicosity by a sodium-dependent carrier. Tyrosine is converted to dihydroxyphenylalanine (DOPA) (the rate-limiting step in the NE synthesis) by the enzyme tyrosine hydroxylase (TH) and finally to dopamine (DA), and a carrier that can be blocked by reserpine transports dopamine into the vesicle. Dopamine is converted to NE in the vesicle by dopamine-β-hydroxylase (DBH). In the adrenal medulla, NE is further converted to epinephrine. TH- and particularly DBH-immunostaining are often used as specific markers for noradrenergic innervation in various organs.

B. Role of Sympathetic Nervous System and Hypothalamo-Pituitary-Adrenal Axis in Maintaining Basal and Stress-Related Homeostasis

Living organisms survive by maintaining an immensely complex dynamic equilibrium of the internal milieu or *homeostasis*, a term coined by Walter Cannon. The systemic sympathetic and adrenomedullary (sympathetic) system (SNS) and the HPA axis are the peripheral limbs of the stress system, whose main function is to maintain both basal and stress-related *homeostasis*. At rest CAs maintain *homeostasis* as major regulators of fuel metabolism, heart rate, blood vessel tone, and thermogenesis. When *homeostasis* is disturbed or threatened by internal or external challenges, both the SNS and HPA axis become activated, resulting in increased peripheral levels of CAs and glucocorticoids that act in concert to keep the steady state of the internal milieu. In the 1930s, Hans Selye defined this reaction as general adaptation syndrome or stress response (Chrousos and Gold, 1992). Any immune challenge that threatens the stability of the internal milieu can be regarded as a stressor; i.e., under certain conditions an immune response can activate the stress system (Fig. 1). In fact, the last 15 years have provided evidence that certain cytokines, and particularly tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 activate both the SNS and the HPA axis (Besedovsky et al., 1986; Chrousos, 1995); (see also Fig. 1, long feedback loop between the immune system and the brain).

Centrally, the two principal components of the general adaptational response are the corticotropin-releasing hormone (CRH) and the locus ceruleus-NE (LC-NE)/autonomic (sympathetic) nervous system (Fig. 1). The CRH system is best characterized in the paraventricular nucleus (PVN) of the hypothalamus. The LC-NE/sympathetic systems are located in the brain stem. Functionally, the CRH and LC/NE/sympathetic systems seem to participate in a positive, reverberatory feedback loop so that activation of one system tends to activate the other as well (Chrousos and Gold, 1992). This includes projections of CRH-secreting neurons from the lateral PVN to the sympathetic systems in the hindbrain, and conversely, projections of catecholaminergic fibers from the LC-NE system, via the ascending noradrenergic bundle, to the PVN in the hypothalamus. Activation of the LC-NE system leads to release of NE from an extraordinarily dense network of neurons throughout the brain, resulting, centrally, in enhanced arousal and vigilance, and peripherally, in increased sympathetic output, i.e., increase of the release of NE from the varicose sympathetic nerve terminals and epinephrine from the adrenal medulla.

III. Autonomic/Sympathetic Innervation of Lymphoid Organs: Nonsynaptic Communication

Many organs of the body, such as heart and the gastrointestinal tract, receive both sympathetic (noradrenergic) and parasympathetic (cholinergic) innervation. It is usual, however, for one type of innervation to predominate over the other. Lymphoid organs, similar to blood vessels, receive predominantly sympathetic/noradrenergic and sympathetic/neuropeptide Y (NPY) innervation (cf. Madden et al., 1995). Histofluorescence studies done

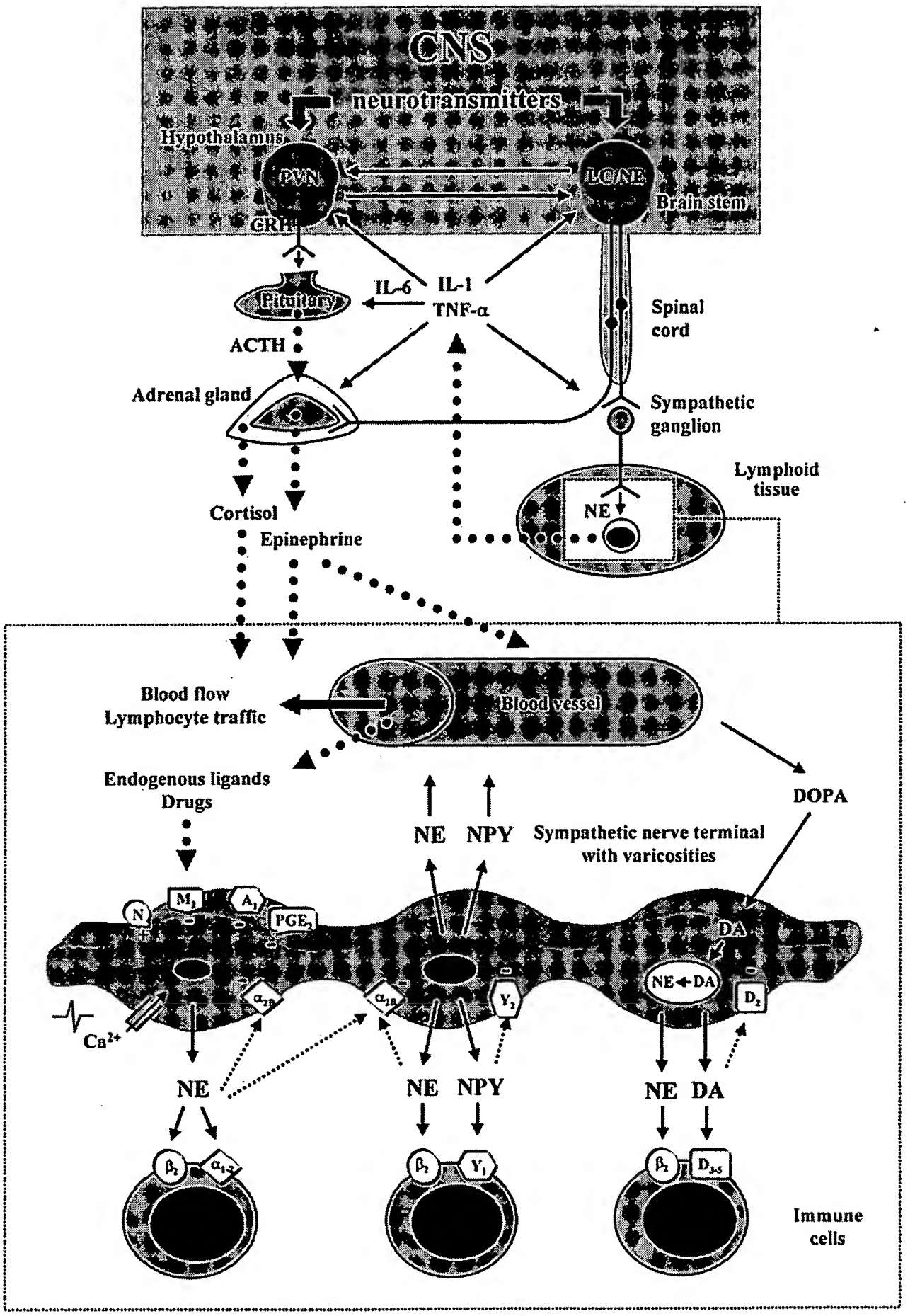

FIG. 1. Role of the SNS and the HPA axis in the bi-directional neuro-immune communication; activation of HPA axis and SNS by certain cytokines, such as IL-1, TNF-α, and IL-6 (feedback loop from the immune system). Simplified scheme of the sympathetic-immune interface (lower panel): role of different presynaptic receptors in modulation of the release of NE from the sympathetic nerve terminals in lymphoid organs; cotransmission of NE and NPY and their role in regulation of blood flow and lymphocyte traffic, cotransmission of NE and DA; role of different receptors on target immune cells in transmitting the message from CNS. Note that immune cells express mostly β-adrenoreceptors, see text for the other type of receptors and conditions that determine their expression. Due to the space restraint and the number of immune cells as targets of the SNS input, different types of lymphoid cells are not depicted, see text for details. Solid lines, neuronal projections; dotted lines, hormonal influences.

since the late 1960s have firmly established the presence of noradrenergic nerves fibers in the lymphoid organs of all species studied (Dahlström and Zetterström, 1965; Zetterstrom et al., 1973; Reilly et al., 1976, 1979; Giron et al., 1980; Williams and Felten, 1981; Bulloch and Pomerantz, 1984; Felten et al., 1985; Kendall et al., 1988). More recently, the presence of noradrenergic innervation in lymphoid tissues was confirmed using

specific immunohistochemistry for TH and DBH (Felten and Olschowka, 1987; Fink and Weihe, 1988; Weihe et al., 1991; Vizi et al., 1995; Kurz et al., 1997). Most of the current knowledge about the innervation of lymphoid organs is based on studies in rodents; relatively few data are available for humans (for reviews see Felten et al., 1985, 1988; Weihe et al., 1991).

A. Innervation of the Thymus

Light microscopic studies using histofluorescence techniques revealed that postganglionic sympathetic nerve fibers enter the thymus along with blood vessels and distribute to the capsular and septal system; these fibers form varicose plexuses in the subcapsular cortex and at the corticomedullary junction; they are extremely sparse in the medulla (Williams and Felten, 1981; Felten et al., 1985; Kendall and Al-Shawaf, 1991; Kranz et al., 1997; Cavallotti et al., 1999). The vast majority of nerve profiles are localized around the vasculature and limited to the cortex. Within the cortex, the densest plexuses are found in the outer cortex, where immature thymocytes reside and develop; the deep cortex, and particularly the corticomedullary junction, an area important for immigration of thymocytes from the thymus, is also richly innervated, mostly along the vasculature. Interestingly, the distribution of mast cells within the thymus parallels the distribution of noradrenergic fibers; the mast cells being usually accumulated in patches immediately adjacent to NE fibers in the perivascular zone (Williams and Felten, 1981). Using specific immunocytochemistry, both TH- (representing the catecholaminergic nature of stained nerve profiles) and DBH-immunostained (demonstrating the noradrenergic feature of stained nerve profiles) nerve fibers (studded with a large number of boutons) are seen in the thymic capsule, subcapsular region, and connective tissue septa (Vizi et al., 1995). The vast majority of immunoreactive nerve profiles are localized around the vasculature. Some TH- and DBH-stained fibers, running along the thymic connective tissue septa, separately from vessels, branch into the cortical parenchyma (Vizi et al., 1995). At the ultrastructural level noradrenergic varicosities are seen in proximity to thymocytes, mast cells, fibroblasts, and eosinophils (Novotny et al., 1990; Vizi et al., 1995). Catecholaminergic nerve fibers also run in close contact to thymic epithelial cells (TEC) that, similar to thymocytes and mast cells, also express β-adrenoreceptors (Vizi et al., 1995; Kurz et al., 1997). Since TECs form the blood-thymus barrier in the outer thymic cortex, these cells may be targets for circulating epinephrine from the adrenal gland or NE released from the perivascular nerves.

B. Innervation of the Spleen

The splenic nerve contains approximately 98% sympathetic nerve fibers (Klein et al., 1982), and most studies suggest that the innervation of the spleen is predominantly sympathetic. Noradrenergic postganglionic innervation originates mainly in the superior mesenteric/celiac ganglion, and the nerve fibers enter the spleen around the splenic artery, travel with the vasculature in plexuses, and continue along the trabeculae in trabecular plexuses (Williams and Felten, 1981). Fibers from both the vascular and trabecular plexuses enter the white pulp and continue mainly along the central artery and its branches. Noradrenergic varicosities radiate from these plexuses into the periarterial lymphatic sheath. The greatest density of noradrenergic fibers in the spleen is associated with the central artery of the white pulp and associated periarterial lymphatic sheath; dense linear arrays of varicosities extend away from the periarterial plexus and travel into the parenchyma (Williams and Felten, 1981; Felten et al., 1985). Sympathetic nerve fibers are present among cells in the T-dependent area; macrophages and B cells residing in the marginal zone and the marginal sinus, the site of the lymphocyte entry into the spleen, also receive NE innervation (Felten et al., 1985; Felten and Olschowka, 1987). Innervation of the B cell-containing follicles is sparse (Williams and Felten, 1981); the red pulp contains scattered fibers, primarily associated with the plexuses along trabeculae and surrounding tissues.

C. Innervation of Lymph Nodes and Tonsils

In lymph nodes, noradrenergic fibers enter at the hilus with the vasculature, and distribute either into a subcapsular nerve plexus or travel with blood vessels through the medullary cords. These fibers run adjacent to both vasculature and lymphatic channels in the medulla and continue with small vessels into the parenchyma of paracortical and cortical regions (Felten et al., 1984; Fink and Weihe, 1988). Within the nodes a large part of the nerves distribute in the medullary and paracortical areas independently of blood vessels (Novotny and Kliche, 1986). Noradrenergic fibers supply paracortical and cortical zones (T cell-rich regions) but are absent from nodular regions and germinal centers, the B cell-containing areas (Felten et al., 1984). In the human palatine tonsils, noradrenergic fibers distribute along the vasculature to form dense perivascular plexuses and single fibers traveling in parafollicular areas. The epithelium and lymphoid nodules are devoid of noradrenergic fibers (Yamashita et al., 1984; Bellinger et al., 1992).

D. Innervation of the Bone Marrow

Data on bone marrow innervation are rare compared with that on other lymphoid tissues. Generally nerves enter the marrow accompanying arteries, travel with the vascular plexuses deep in the marrow, arborize in surrounding parenchyma, and end among hemato- and

lymphopoietic cells. Most of the nerves supply the arterial component of the marrow's circulation, but there is a substantial innervation of the sinusoidal parts and parenchymal elements where they may influence hematopoiesis and cell migration (Felten et al., 1988). Recently, immunoreactivity for TH, a marker for noradrenergic nerves was found around large vessels, with occasional TH-positive fibers extending into the bone marrow of mice. NPY immunopositive fibers were smaller and less abundant than those for TH but were found in a similar pattern (Tabarowski et al., 1996). Sensory nerves containing substance P (SP) and calcitonin gene-related peptide (CGRP) also innervate the bone marrow. Studies in rodents indicate that the development of the innervation of bone marrow occurs late in fetal life, just before the onset of hemopoietic activity (Calvo and Haas, 1969; Miller and McCuskey, 1973).

E. Innervation of Mucosa-Associated Lymphoid Tissues

Gut-associated lymphoid tissue (GALT) and bronchus-associated lymphoid tissue (BALT) receive both sympathetic and peptidergic innervation (Felten et al., 1985; Weihe et al., 1991). The nerve network within mucosal tissues is very extensive (Cooke, 1986; Bienenstock et al., 1989). It has been calculated that the number of nerve cell bodies present in the gastrointestinal tract is equivalent to that found in the spinal cord (Furness and Costa, 1980). Neuropeptides are found in very large amounts in these tissues, particularly SP, vasoactive intestinal peptide (VIP), and somatostatin (Cooke, 1986). Although this issue is not extensively studied, the available information suggests that in GALT including Peyer's patches that represent clusters of lymphoid nodules in the intestines, and the appendix of the rabbit, varicose noradrenergic fibers arborize profusely in the interdomal region of the lamina propria. Here, fibers follow small vessels and branch freely in the parenchyma among fields of lymphoid cells, usually not in association with blood vessels (Bellinger et al., 1992). Nerves predominate in T cell zones of lymphoid aggregates, where they contain neuropeptides and the sympathetic neurotransmitter NE. Interestingly, as in other lymphoid tissues, intestinal mucosal mast cells lying immediately under the epithelium are apparently selectively associated with enteric nerves, and this is not a random finding (Cooke, 1986). In these tissues, the noradrenergic varicosities are also adjacent to serotonergic enterochromaffin cells (Felten et al., 1985). In addition, the nasal mucosa receives tonic discharges from the sympathetic nerves but not from the parasympathetic nerves. Although recent evidence suggests that sympathetic nerve stimulation may up-regulate immunoglobulin (Ig)A secretion in the submandibular glands (Carpenter et al., 1998), as a whole there is almost complete lack of information of how the sympathetic innervation and endogenous CAs may affect mucosal immunity. Interestingly, mucosal immune responses tend to bias toward T helper (Th) 2 responses (Ernst et al., 1999). Since CAs and the mast-cell product histamine mediate a Th2 shift (Elenkov et al., 1996, 1998; Wilder and Elenkov, 1999) (see *Section X.*) an interesting hypothesis to pursue is whether locally released biogenic amines might contribute to the dominance of the Th2 responses observed in these tissues.

F. Coexistence Patterns

Double immunofluorescence reveals the *coexistence* of DBH-(noradrenergic) and NPY-like immunoreactivity in sympathetic nerve fibers of lymphoid organs (Lundberg et al., 1988). Klein et al. (1982) have demonstrated that NE is also *co-stored* with opioid peptides in the population of large dense-cored noradrenergic vesicles of the spleen, although no evidence, so far, is available of co-release of opioids and NE from the sympathetic nerve fibers of lymphoid organs.

G. General Pattern of the Autonomic/Sympathetic Innervation of Lymphoid Organs

Sympathetic/noradrenergic and sympathetic/NPY postganglionic nerve fibers innervate both the smooth muscle of the vasculature and the parenchyma of specific compartments of primary and secondary lymphoid organs (Felten et al., 1985). Both noradrenergic and NPY nerve fibers and their varicosites do travel in plexuses that run adjacent to smooth muscle cells of the blood vessels in lymphoid organs; it is therefore possible that both NE and NPY, released from these fibers, play a role in controlling blood flow to these organs and may influence lymphocyte traffic (Fig. 1). However, noradrenergic fibers also travel with smaller vessels that are devoid of smooth muscle cells. In addition, some noradrenergic fibers are present in the parenchyma of lymphoid organ tissue that are not associated with blood vessels (Felten et al., 1985; Vizi et al., 1995). Thus, NE released from perivascular or parenchymal nerve fibers may affect lymphoid cells and exert an immunomodulatory role. Noradrenergic innervation of lymphoid tissue appears to be regional and specific; generally, zones of T cells, macrophages, and plasma cells are richly innervated, while nodular and follicular zones of developing or maturing B cells are poorly innervated (Felten et al., 1985). The main target cells of the noradrenergic innervation appear to be immature and mature thymocytes, TEC, T lymphocytes, macrophages, mast cells (Blennerhassett and Bienestock, 1998), plasma cells, and enterochromaffin cells. Noradrenergic nerve fibers, particularly in the thymus, are closely associated with mast cells in both perivascular and parenchymal zones, suggesting a possible humoral role for NE and histamine in the development of T cells in the thymus. Noradrenergic innervation is present early in the development, and

their arrival generally precedes the development of the cellular compartment of the immune system suggesting a role for NE in maturation of the immune system (see *Section VII.*).

H. Spatial Relationships with Peptidergic Innervation

In addition to the autonomic/sympathetic innervation, all lymphoid organs also receive sensory peptidergic innervation that is confined mostly to the parenchyma (Weihe et al., 1991). The most abundant peptides are tachykinins (substance P, neurokinin A), CGRP, and vasoactive intestinal polypeptide/peptide histidine isoleucine (VIP/PHI). Double immunofluorescence reveals *coexistence* of tachykinins with CGRP and of TH and NPY. The coexistence of peptides with peptides and of NPY with markers of the catecholamine pathway conforms to the general scheme described for the peripheral innervation of other organs. Similar to other organs, the tachykinins/CGRP fibers most likely have sensory origins. As a general pattern, and as in the case of noradrenergic innervation, a close spatial relationship between peptidergic nerve fibers and mast cells, T cells and macrophages is observed (Weihe et al., 1991). Peptidergic nerves also appear to be sparse in pure B cell regions. Neuromast cell contacts are relatively often seen in all lymphoid organs, with the exception of the spleen (Weihe et al., 1991). Mast cells bear receptors for SP that, after stimulation, trigger release of histamine and other factors such as leukotrienes; NE, however, through stimulation, respectively of α- and β_2-adrenoreceptors is known to stimulate and inhibit, respectively, the release of histamine from mast cells (Kaliner et al., 1972; Tomita et al., 1974). Thus, apart from their direct immunomodulatory effects, NE released form postganglionic noradrenergic nerve terminals or SP antedromically released from sensory nerves may exert an important immunomodulatory role, indirectly, via modulation of histamine release from mast cells in the parenchyma of lymphoid organs.

I. Neuroimmune Connection in Nonorganized Lymphoid Compartments

Neuromast cell connections and neuromacrophage connections, as well as neuro-T cell contacts, are not restricted to the preformed lymphoid organs and tissues, but are also regularly encountered in virtually all somatic and visceral tissues (Weihe et al., 1991). T cells, macrophages, and mast cells are regularly seen in any peripheral nerve and in both sympathetic and sensory ganglia. In the skin postcapillary venules, macrophages, mast cells, and peptidergic nerves, stained for tachykinins and CGRP, form a typical quadruplet, whereas in the outer wall of larger blood vessels, TH/NPY fibers also join in to form neuromast cell and neuromacrophage interrelations. Furthermore, close interrelations but no coincidence of TH/NPY-immunoreactivity and of SP/CGRP fibers are frequently observed in perivascular regions (Weihe et al., 1991).

IV. Nonsynaptic Release of Norepinephrine in Lymphoid Organs: Presynaptic Modulation and Effect of Drugs

A. Evidence for Neural Release of Norepinephrine (and Dopamine) in Lymphoid Organs

Whereas endocrine signaling depends on blood-borne access of hormones to immune cells, neurotransmitter signaling depends on local availability of the specific neurotransmitter from neural release. Neural release is achieved when the propagated electrical signal reaching the axon terminal triggers a depolarization that causes the release of neurotransmitter, provided that $[Ca^{2+}]_o$ is available (Fig. 1). Recently, several studies using blood-perfused pig spleen in vivo, or medium-perfused Atlantic cod and rat spleen in vitro, demonstrated that the sympathetic nerve terminals in the spleen are able to store, take up, and, subsequently, release NE in response to field stimulation (Lundberg et al., 1989b; Ehrenstrom and Ungell, 1990; Elenkov and Vizi, 1991). Using an in vivo microdialysis technique NE levels can be monitored in the spleen of conscious rats (Shimizu et al., 1994). Splenic content of NE has been depleted up to 95% (depending on the species and the strain) by the noradrenergic neurotoxin 6-hydroxydopamine (6-OHDA), indicating that most splenic NE is of neuronal origin (cf. (Felten and Olschowka, 1987). More recently we have demonstrated that the rat thymus takes up and releases substantial amounts of NE (Hasko et al., 1995b; Vizi et al., 1995). The release of NE in lymphoid organs, both in vitro and in vivo, is $[Ca^{2+}]_o$- and frequency-dependent and a tetrodotoxin-sensitive process, thus indicating its neuronal origin. In addition, the inhibition of vesicular storage of CAs by reserpine results in blockade of the release of NE evoked by field stimulation (Vizi et al., 1995), suggesting that the release of NE in the thymus is of vesicular origin.

The existence of DA receptors on several cell lines of the immune system, including those found in the spleen, has been shown (Santambrogio et al., 1993), and functional studies have suggested that DA receptors on immunocytes of the spleen may have a role in the regulation of immunocompetence (Won et al., 1995). The possible source of immunoregulatory DA in the spleen has been found (Bencsics et al., 1997b). In view of the lack of dopaminergic innervation, plasma DA (Van Loon, 1983) or DOPA (Kvetnansky et al., 1992) could be a candidate (see Fig. 1).

It was shown (Bencsics et al., 1997b) that the noradrenergic axon terminals in the spleen are able to take up DA from the circulation, convert it in part into NE, and release it as both DA and NE in response to neural activity. The ratio of [^{3}H]DA and [^{3}H]NE in the spleen loaded with [^{3}H]DA was found to be dependent on both

temperature and time of loading, and could be modulated by various drugs such as desmethylimipramine, a NE uptake blocker, and disulfiram or fusaric acid, dopamine β-hydroxylase inhibitors. This phenomenon may reveal a new mechanism by which immunocytes in the spleen can be regulated by the neuroendocrine system. Therefore, it is suggested that under physiological conditions, the source of DA being taken up by noradrenergic terminals can be circulating DA, especially during stress, since exposure of an organism to any of a variety of stressors that increase sympathetic tone is accompanied with an increase in plasma concentrations of DA (Van Loon, 1983).

Electrical stimulation of the splenic nerves induces frequency-dependent output of NPY-like immunoreactivity and NE, suggesting co-release of these neurotransmitters (Lundberg et al., 1989c) (Fig. 1). As in other organs, the classical neurotransmitter NE is preferentially released from small storage vesicles at low frequency, whereas at higher frequency, an increased proportion of large dense-cored vesicles release both NPY and NE (Lundberg et al., 1989c). Thus, during resting conditions little NPY is released, whereas in situations of high sympathetic activity, the contribution of NPY becomes more important. Although in many tissues, ATP is co-stored with NE and NPY in the large dense-cored vesicles of sympathetic nerve terminals, so far, no evidence is available to support release or co-release of ATP with NE from these terminals in lymphoid organs.

B. Norepinephrine Is Released and Affects Immune Cells Nonsynaptically

Since Sherrington's classic work in 1906 it has become a doctrine of neurophysiology that the synapse, a part of the surface of separation between neurons, is the primary site of neuronal information processing (Tansey, 1997). Thus, the chemical substances are released by depolarization from the axon terminals across the synaptic cleft (about 15–100 nm) and act on the postsynaptic membrane equipped with receptors. Now, however, it is clear that, in contrast to some regions of the CNS and particularly to the neuromuscular junction, where classical synapses are observed, postganglionic neurons in the periphery innervating blood vessels, vas deferens, and smooth muscle terminate in a network of varicose areas (boutons en passant) that lack synaptic contact with their target cells (cf. Vizi 1984a,b, 2000; Vizi and Labos, 1991). Similarly, in Auerbach' plexus of the gut, or the cerebral cortex where noradrenergic axon terminals do not make synaptic contacts with cholinergic axon terminals, NE should diffuse over relatively long distances before modulating the release of acetylcholine from the cholinergic neurons. It has been shown (cf. Vizi and Kiss, 1998; Vizi, 2000) that in the CNS the monoamines (NE, dopamine, serotonin) released from nonsynaptic varicosities into the extracellular space, diffusing far away from the release sites, make functional interactions with other neurons without making synaptic contacts. NE exerts its effect through nonsynaptic, high-affinity α_2-ARs (Vizi, 2000). Thus, many of the neurotransmitters, especially the monoamines and peptides, show a release profile that is halfway between specific synaptic neurotransmission and relatively nonspecific endocrine secretion. This release profile is referred to as "nonsynaptic" (Vizi, 1979, 1980, 1984, 1991, 2000; Vizi and Labos, 1991; Vizi and Lendvai, 1999).

Nonsynaptically, the neurotransmitter is released from free nerve endings into a large extraneuronal space, with no postjunctional specializations, and hence, the neurotransmitter diffuses a considerable distance (sometimes this could be more than 1 μm) before interacting with its receptors on target cells (Vizi, 1980, 1984a,b, 2000; Vizi and Labos, 1991; Vizi and Kiss, 1998). Conversely, in the case of classical synaptic neurotransmission, e.g., at the neuromuscular junction, the distance between release sites and the postsynaptic receptor is much shorter. The nonsynaptic neurotransmission is relatively *slow* and *tonic*, while the synaptic neurotransmission is *short* and *phasic* (Table 1).

This slow interaction should be distinguished from the very slow, hormone-mediated humoral control. In the time domain from 100 msec to several minutes such "slow" tuning effects seem very conceivable; moreover, they would appear to be useful in controlling autonomic functions and the balance between the sympathetic and parasympathetic nervous system.

Although some occasional "synaptic-like" contacts have been described in the spleen (Felten and Ol-

TABLE 1
Differences between the classical synaptic and the nonsynaptic interaction[a]

	Synaptic	Nonsynaptic
Type of communication	One-to-one	One-to-many
Delay	Short (100–200 msec)	Long (>1 s)
Action (duration)	Short (msec) and phasic	Long (min) and tonic
Discrimination		Dependence of the presence of receptors
Sensitivity of receptors	Low affinity	High affinity[b]
Agonist concentration in the vicinity of receptors	mM	nM–μM
Chemical agent has to	Cross the gap (5–20 nm)	Diffuse distances of some micrometers
Morphological characteristics of presynaptic modulation	Axo-axonic synapse (post-junctional specializations)	Free nerve endings, varicosities (no post-junctional specializations) mismatch of release site/receptor

[a] Modified from Vizi and Labos, 1991 and Vizi and Kiss, 1998.
[b] For an explanation see Vizi, 2000.

schowka, 1987), most of the ultrastructural studies reveal that noradrenergic fibers in lymphoid organs are confined to the connective tissue septa and do not make "classical" synaptic contacts with target cells. Thus, for example in the thymus, some of these connective tissue septa are extremely fine, sometimes 1 μm or less. They invest thymic "microlobules" and, thus, penetrate far into the parenchyma (Novotny and Kliche, 1986; Novotny et al., 1990; Vizi et al., 1995). These septa are clearly delineated in the juvenile animals, but indistinct in the aged rats, thus creating sometimes the "spurious impression" using light microscopy that parenchymal cells receive direct innervation (Novotny et al., 1990). In fact, ultrastructural studies failed to observe classical synapses between thymocytes and neuronal elements in the rat thymus (Novotny and Kliche, 1986; Novotny et al., 1990; Saito, 1991; Vizi et al., 1995). This is substantiated by the observation that noradrenergic nerve fibers, along the thymic tissue septa, branch into the parenchyma and some of the septal NE nerve terminals are about 200 nm from the surface of thymocytes (Vizi et al., 1995).

Similarly, in the spleen, a recent ultrastructural study reveals that the innervation is confined to the connective tissue system, which includes the capsulo-trabecular, peri-vascular and reticular systems. All components of the connective tissue system are continuous with each other, and the nervous elements appearing in the reticular system are the elongated ones from other connective tissue systems, especially peri-vascular connective tissue. It has been proposed that the minute connective tissue space of the reticular system serves as a NE canal. NE is released from the noradrenergic nerve varicosities in this tissue, diffuses, and is temporary stored in this enclosed space (Saito, 1991). The reticular system in the spleen divides the parenchyma into small nonendothelial vascular spaces with its own meshwork, and free mobile immunocytes stagnate in these spaces. This stagnation of the mobile immunocytes and the presence of the noradrenergic nerves in the NE canals provide an opportunity for the immunocytes and nerves to meet each other (Saito, 1991).

The nerve-target interactions in lymphoid organs have not been studied in detail. However, as in general, in the periphery, it appears that in lymphoid organs NE is also released *nonsynaptically*, i.e., from varicose axon terminals, which do not make synaptic contacts. Moreover, NE released from perivascular or connective tissue septa plexuses of nerve terminals diffuse away through surrounding adventitia or collagenous fibrils, in a paracrine fashion. Thus, adrenoreceptors on immune cells are targets of remote control, and, thus, NE, may play a modulatory role in signal transmission at the sympathetic-immune interface (Vizi et al., 1995). Similar *nonsynaptic* transmission may operate in the blood vessel wall (between varicose nerve terminals and smooth muscle cells) of these organs, where NE and NPY might be involved, as already mentioned, in regulation of blood flow and lymphocyte traffic. This is substantiated by a recent ultrastructural observation that the distance between a naked axon and a smooth muscle cell of arterioles and muscular venules in the lymph nodes ranges from 100 to 800 nm (Villaro et al., 1987).

C. Presynaptic Modulation of Norepinephrine Release in Lymphoid Organs: Effect of Drugs

The release of transmitters from varicose axon terminals in response to action potentials is a very random process subject to presynaptic modulation through stimulation of receptors located on the varicose axon terminals (Vizi, 1979; Starke, 1981; Stjärne et al., 1990; Vizi et al., 1991; Vizi and Labos, 1991). These presynaptic receptors can be classified as *auto-*, *homo-*, and *heteroreceptors* depending on the origin of the transmitters and localization of the receptors. *Autoreceptors* receive messages by transmitter released from the same neuron. They are involved in negative or positive feedback modulation. *Homoreceptors* receive signals from the adjacent neuron, whose transmitter is the same as the neuron where the homoreceptors are located. The homoreceptors can also serve as autoreceptors. *Heteroreceptors* are located on axon terminals that do not manufacture transmitters capable of exerting an effect on these receptors. These receptors receive messages by transmitters from other neurons.

Whereas autoreceptors play a role in keeping the release constant, heteroreceptors are involved in interneuronal communication, in *cross-talk* between neurons at the presynaptic level. Since none of the transmitter/modulator substances tested have any receptor-mediated effect on the propagation of action potentials in nerve trunks, the site of their action is on the axon terminals. The activation of presynaptic receptors located on the axon terminals may interfere with processes involved in the transmitter release. The significance of the presynaptic modulation is that the input to the postsynaptic cell can be selectively modulated without changing the excitability of the effector cell as a whole (Vizi et al., 1991). In many tissues, the noradrenergic nerve terminals are equipped with auto-, homo-, and heteroreceptors sensitive to different endogenous and exogenous ligands or drugs (Table 2).

Both in the periphery and some regions of the CNS, NE released from noradrenergic axon terminals reduces its own release evoked by the subsequent stimuli (negative-feedback modulation) through stimulation of presynaptic α_2-adrenoreceptors (cf. Vizi, 1979; cf. Starke, 1981). α_2-ARs have been divided into three subtypes (α_{2A},α_{2B}, and α_{2C}) on the basis of pharmacological and molecular cloning evidence (Bylund et al., 1994; Kable et al., 2000). The negative feedback phenomenon also operates in lymphoid organs. We have demonstrated that both in the rat spleen and thymus, in an in vitro perfusion system, the application of highly selective α_2-AR

TABLE 2
Role of some presynaptic inhibitory and stimulatory receptors in Ca^{2+}-dependent transmitter release from noradrenergic axon terminals in the CNS and periphery[a]

Receptor Ligand	Receptor Subtype	Effect
Norepinephrine	α_2[b] (A and C)	Inhibition
	β_2 (spleen[b])	Potentiation
Acetylcholine	M_1	Potentiation
	M_2[b] (M_3)	Inhibition
	N[b] (neuronal)	Potentiation
Neuropeptide Y	Y_2 (spleen[b])	Inhibition
Dopamine	D_2 (spleen[b])	Inhibition
Adenosine	A_1[b]	Inhibition
ATP	P_2	Potentiation
Opioid peptide[b]	μ	Inhibition
	δ	Inhibition
	κ	Inhibition
Prostaglandin	PGE_2 (thymus[b])	Inhibition
Serotonin	5-HT_{1B}	Inhibition

[a] Modified from Vizi et al. (1991).
[b] Receptors whose function has also been established in the spleen and the thymus (see text).

antagonists and prazosin, an α_{2C}-subtype selective AR antagonist (cf. Docherty, 1998) results in a significant increase in stimulation-evoked release of NE (Elenkov and Vizi, 1991; Vizi et al., 1995; Hasko et al., 1995b). The release is enhanced because it escapes from the negative feedback modulation exerted by NE itself. Vice versa, when a selective α_2-AR agonist is applied, the release of NE is inhibited (Elenkov and Vizi, 1991). This indicates that the noradrenergic axon terminals in the rat spleen and thymus are equipped with presynaptic α_{2C}-ARs (Table 3) and that the release of NE from these noradrenergic nerve terminals is under *tonic* inhibition by the endogenously released NE.

The noradrenergic nerve terminals of the spleen and the thymus are also equipped with presynaptic M-muscarinic-, N-nicotinic-, P_1-purinergic (A1) and PGE_2-prostaglandin E_2 heteroreceptors (Elenkov and Vizi, 1991; Hasko et al., 1995b). Stimulation of presynaptic M-muscarinic (by acetylcholine or selective drugs), P_1-(A1, adenosine-sensitive), and PGE_2 receptors reduces the release of NE, whereas the stimulation of presynaptic N-nicotinic (acetylcholine, nicotine) receptors releases NE from the varicosity (cf. Wonnacott, 1998; Vizi and Lendvai, 1999) and increases the stimulation-evoked release of NE, i.e., NE released in response to neuronal firing. Additional evidence indicates that in the spleen opioid receptors (the subtype has not been clarified), NPY2, β_2-ARs, and D2 receptors (Gaddis and Dixon, 1982; Lundberg et al., 1989a; Sato et al., 1992; Bencsics et al., 1997b) can also participate in the modulatation of the release of NE (Table 2). Through these receptors the release of NE (i.e., the message from the CNS to these lymphoid organs) can be modulated by endogenous ligands (e.g., NE, epinephrine, dopamine, NPY, opioids, prostaglandin E2, adenosine, etc.) or by drugs present in the circulation (Fig. 1).

D. Release of Neuropeptide Y and Its Action on Immune Cells

NPY is a 36-amino acid peptide that acts as a neurotransmitter and neuromodulator in the CNS and the peripheral nervous system. NPY-positive nerve fibers are present in all lymphoid organs (Lundberg et al., 1988; Weihe et al., 1989; Weihe et al., 1991). These fibers predominantly supply the vasculature, where they mainly occur as perivascular plexuses and both NE and NPY, released from these fibers, control blood flow and may affect lymphocyte traffic. They branch off only rarely to run into the lymphoid parenchyma (Felten et al., 1985). Evidence was obtained that both NE and NPY are released together (Lundberg et al., 1989c) (Fig. 1). A few reports suggest that lymphoid cells might also express NPY receptors. Thus, in vitro, NPY suppresses human NK cell activity (Nair et al., 1993), whereas low levels of mRNA for NPY-Y1 was found in rat splenic lymphocytes (Petitto et al., 1994). Thus, overall, the precise expression and function of α-ARs, DA, and NPY receptors on different lymphocyte/leukocyte subpopulations await further studies.

V. Systemic and Local Effects of Cytokines on Sympathetic Nervous System Activity

A. Systemic Effects: Long Feedback Loop between the Immune System and the Brain

In the 1970s Besedovsky and coworkers provided the first evidence that the immune system and its products can signal the CNS. Thus, immunization with sheep red blood cells (SRBC), administration of lymphocyte-conditioned medium or IL-1 in animals, induced an increase of plasma corticosteroid levels, altered the activity of hypothalamic noradrenergic neurons, and dropped the content of NE in the spleen (Besedovsky et al., 1979, 1983, 1986; Del Rey et al., 1982). Later, it become clear

TABLE 3
Subtype of α_2-adrenoreceptor responsible for the negative feedback modulation of NE release in the periphery and the central nervous system

	Organ	Subtype of α_2-AR	References
Periphery	Spleen	α_{2C}[a]	Elenkov and Vizi, 1991
	Thymus	α_{2C}[a]	Hasko et al., 1995b
	Ileum	α_{2C}[a]	Blandizzi et al., 1993
Central nervous system	Cortex	α_{2A}	Trendelenburg et al., 1996
	Hippocampus	α_{2A}	Kiss et al., 1995
	Spinal cord	α_{2A}	Umeda et al., 1997

[a] Earlier it was designated as α_{2B}-ARs, because prazosin increased the release of NE, but it has recently been shown that prazosin is an α_1 and $\alpha_{2B/C}$ antagonist (cf. Docherty, 1998), and it was shown, using gene substitution/knockout mice, that α_{2B}-ARs are located postsynaptically (cf. Hein et al., 1998). Therefore it seems very likely that the α_{2C}-subtype of presynaptic α_2-ARs is involved in the negative feedback modulation of NE release.

that during an immune response certain cytokines, such as IL-1, IL-6, and TNF-α can signal the brain, which through a complex CRH-dependent pathway, triggers activation of both the SNS and the HPA axis (Berkenbosch et al., 1987; Sapolsky et al. 1987; Dunn, 1988; Elenkov et al., 1992b; Kovacs and Elenkov, 1995). Thus, administration of IL-1 in the periphery increases the turnover of NE in the hypothalamus (Dunn, 1988, 1998; Zhang et al., 1998; Dunn et al., 1999) and raises peripheral plasma (Berkenbosch et al., 1989) and CNS (Dunn et al., 1999) NE metabolism and extracellular levels; intracerebroventricular (i.c.v.) and peripheral injection of interferon (IFN)-α or IL-1β produces a long-lasting increase of the sympathetic activity of the splenic nerve and an increased turnover of NE in the spleen (Katafuchi et al., 1991); as a result, the release of NE in the spleen is enhanced, as indicated by a recent in vivo microdialysis study (Shimizu et al., 1994). It has been shown (Zhang et al., 1998) that i.c.v. infusion of CRF increases extracellular concentration of NE in the hippocampus and cortex as determined by in vivo voltammetry. Thus, the SNS, similar to HPA axis (Besedovsky et al., 1986), is involved in a long feedback loop between lymphoid organs and CNS. The afferent limb of this loop seems to operate by blood-borne cytokines that, via circulation or through the afferents of the vagus nerve (Maier et al., 1998), activate the central components of the stress system. The efferent loop consists of the SNS, its projections to lymphoid organs and the release of NE from the sympathetic nerve terminals in these organs. This feedback loop seems to be a *regulatory one*, since i.c.v. infusion of IL-1β or IFN-α rapidly decreases peripheral and splenic NK cell activity and suppresses the mitogen response and the production of IL-1 and IL-2 of splenic cells (Sundar et al., 1989; Brown et al., 1991). These effects depend upon intact splenic sympathetic innervation (Sundar et al., 1990; Brown et al., 1991), whereas direct splenic nerve stimulation results in reduced NK activity (Katafuchi et al., 1993).

Distinct functional pathways exist within the ANS and SNS, i.e., ANS consists of a set of subdivisions, innervating different effectors, each of which is controlled by specific reflex mechanisms related to the function of the effector. This has been firmly established for the lumbar sympathetic nervous system to skin, skeletal muscle and viscera, and for the thoracic sympathetic outflow to the head and for several parasympathetic systems (Janig and McLachlan, 1992a,b).

The function-specific unit(s) that are involved in the activation of the SNS during an immune response, their properties and behavior, are not fully understood. However, the above-mentioned observations suggest that the inflammatory/immune response may actually activate different pathways of SNS, as compared with other stressors or stimuli. This is substantiated by the observation that the content of NE in the rat spleen drops during the peak of the immune response to immunization with SRBC; however, the content of NE in the heart remains unchanged (Besedovsky et al., 1979). Similarly, an intravenous administration of IL-1β results in a dose-dependent long-lasting increase of the sympathetic activity of the splenic and adrenal nerves; however, the activity of renal nerves shows only a transient increase, which is followed by a long-lasting suppression (Niijima et al. 1991; Elenkov, 1993). Endotoxin impedes vasoconstriction in the spleen (Rogausch et al., 1997). A recent study by Terao et al. (1994) demonstrated that intraperitoneal or i.c.v. injection of IL-1 accelerated NE turnover in the spleen, lung, diaphragm, and pancreas without appreciable effects in other organs examined. IL-6, however, did not affect NE turnover in every organ examined, in contrast to its substantial effect on plasma corticosterone levels. Thus, it appears that each immune response, similar to different stressors (see Pacak et al., 1998), may have its own specific central neurochemical and peripheral neuroendocrine "signature".

B. Local Effects of Tumor Necrosis Factor-α and Interleukin-1

The above-mentioned data suggest that systematically administered TNF-α and IL-1 trigger centrally the sympathetic output that results in an increase of NE turnover in several lymphoid and nonlymphoid organs in the periphery. In apparent contrast, the local effect of these cytokines might be different. Thus, we have shown that TNF-α inhibits the stimulation-evoked release of NE from isolated rat median eminence (ME) (Elenkov et al., 1992a). The ME is a hypothalamic structure not protected by blood-brain barrier; here neurosecretory projections, such as CRH from the PVN, terminate and control hormone secretion from the anterior pituitary. Noradrenergic varicosities in the ME are not equipped with α_2-presynaptic-ARs (Vizi et al., 1985). However, this hypothalamic structure expresses high-density α_2-ARs that are exclusively located on the axon terminals of the hormone-containing neurons (Plotsky et al., 1989). Because NE released in this region might exert tonic inhibitory control on hormone release through stimulation of α_2-ARs (Vizi et al., 1985; Plotsky et al., 1989), it was suggested that TNF-α, by inhibiting NE release (i.e., by disinhibition of this control), might trigger an increase of CRH release and subsequently an increase of ACTH from the anterior pituitary (Elenkov et al., 1992a). Recently, evidence was obtained that TNF-α was also able to inhibit the release of NE in rat hippocampus (Ignatowski and Spengler, 1994; Ignatowski et al., 1997). The regulation of NE release in this structure by TNF-α appears to be associated with an alteration of α_2-ARs responsiveness. Administration of the antidepressant desipramine to rats for 2 weeks transformed the presynaptic TNF-α response. It was suggested that this mechanism might play a role in the delayed clinical effect of this drug (Ignatowski and Spengler, 1994). In contrast, local administration of IL-1β by intracerebral

microdialysis technique in rats resulted in an elevation of NE concentration in the medial prefrontal cortex (Kamikawa et al., 1998). Furthermore, evidence was obtained in this study indicating that IL-1β induces a rise in NE levels by activation of the glutamatergic system and the glutamate-induced increases in prostanoids and nitric oxide (NO).

In the periphery, Hurst and Collins (1993, 1994) reported that both IL-1 and TNF-α inhibited the release of NE from longitudinal muscle-myenteric plexus preparations of rat jejunum. Interestingly, both IL-1 and TNF-α also inhibited the stimulation-evoked (i.e., neural) release of NE from superfused isolated atria from humans and mice; the effect of IL-1 was suggested to be mediated through formation of prostaglandins (Foucart and Abadie, 1996; Abadie et al., 1997). These effects might have important clinical implications. It appears that the heart is a TNF-α-producing organ; both myocardial macrophages and cardiac myocytes themselves synthesize TNF-α. Accumulating evidence indicates that myocardial TNF-α is an autocrine contributor to myocardial dysfunction and cardiomyocyte death in ischemia-reperfusion injury, sepsis, chronic heart failure, viral myocarditis, and cardiac allograft rejection (Meldrum, 1998). Thus, the effect of TNF-α on NE release in the heart might interfere with these pathologic conditions and represents a realistic goal for clinical medicine.

VI. Expression of Adrenoreceptors on Lymphoid Cells: Signal Transduction

A. Expression and Distribution of Adrenoreceptors on Lymphoid Cells

NE and epinephrine mediate their effects on target cells via stimulation of two principal receptors: *alpha* (α) and *beta* (β) adrenergic receptors (ARs). β-ARs are now subdivided into β_1, β_2, and β_3 subtypes, whereas α-ARs are subdivided into two types, α_1 and α_2, each of which are now known to comprise additional subtypes. Virtually all lymphoid cells express β-ARs, with the exception of T helper (h) 2 cells (see below). Several studies, using human isolated peripheral mononuclear cells suggest that the β-ARs numbers, differ between different types of lymphoid cells. The precise ordering of β-AR density among T cells, B cells, and monocytes is somewhat inconsistent. One study shows that the specific order of receptor density is NK cells > $CD14^+$ monocytes > $T_{cytotoxic}$ (Tc) ~ B cells > Th cells (Maisel et al., 1990a), whereas another study demonstrates slightly different order NK cells > Tc ~ B cells ~ monocytes > Th cells (Maisel et al., 1989). Lymphocyte and NK cell β-ARs belong to the β_2-AR subtype, and the receptor number ranges from about 4000 receptors/cell for B cells and NK cells, approximately 1800 receptors for Tc, to between 200 and 750 binding sites for Th cells (Khan et al., 1986). The discrepancy in receptor number in the above studies is most likely atttributed to the small number of subjects employed in some of them. When a larger group of 28 subjects of either sex was studied, Maisel et al. (1989) confirmed that lymphocyte subsets differ in their β_2-AR density, with NK cells having the greatest and helper T cells having the lowest number of receptors; Tc, B cells, and monocytes had an intermediate number of receptors. Importantly, a recent study in mice demonstrates β_2-AR expression on Th1 cells, but not on Th2 cells (Sanders et al., 1997). This phenomenon may provide a mechanistic basis for differential modulation of Th1 and Th2 functions by CAs, discussed below. Other lymphoid cells also express β_2-ARs, including thymocytes, TEC, neutrophils, basophils, and eosinophils (Plaut, 1987; Yukawa et al., 1990; Kurz et al., 1997). The number of β_2-ARs appears to vary during the life span (stem cell to mature activated immunocyte). For example, in mice, immature thymocytes probably have a lower number of β_2-ARs than more mature T cells (Radojcic et al., 1991).

The coupling between β_2-AR and adenylate cyclase may also differ in various lymphocyte subsets; in other words, high β_2-AR density does not necessarily mean high cAMP response after stimulation of these receptors. Thus, some subsets, such as B cells may have a high prevalence of low affinity receptors, which are weakly coupled to the adenylate cyclase. In contrast, NK cells, Tc, and monocytes possess a substantial number of ARs, probably in a high-affinity state that are very responsive to β-AR stimulation with regard to cAMP response. In fact, two recent studies demonstrate that NK cells, Tc, and monocytes are very responsive to β-AR stimulation, with regard to cAMP accumulation; however Th and B cells showed only a modest response (Maisel et al., 1989; Knudsen et al., 1995).

The presence of α_2-ARs on peripheral blood mononuclear cells (PBMC) that contain mainly lymphocytes and monocytes, is controversial. Since platelets express α_2-ARs, and mononuclear preparations often contain platelets, the binding of specific α_2-ligands might be due to contamination with platelets. Thus, no α_1- and α_2-ARs could be identified on platelet-depleted mononuclear cells (Casale and Kaliner, 1984), in contrast to preliminary reports showing the presence of α_2-ARs on PBMC. However, some functional studies implicate both α_1- and α_2-ARs in modulation of some immune parameters (see below). Thus, alternatively, α-ARs probably are not expressed under normal conditions on PBMC (lymphocytes, monocytes); however, they may be expressed in certain lymphoid compartments, such as alveolar and peritoneal macrophages, or hematopoietic cells (see below), or under certain pathologic conditions. One such condition might be polyarticular juvenile rheumatoid arthritis (JRA). Thus, PBMC from patients with polyarticular JRA, in contrast to healthy volunteers, respond to α_1 receptor stimulation with an increased production of IL-6 (Heijnen et al., 1996).

In recent years the expression of dopamine D3, D4, and D5 receptors was demonstrated using molecular

biological techniques (Takahashi et al., 1992; Nagai et al., 1993, 1996; Bondy et al., 1996). Also, recently radioligand binding studies provided additional evidence that peripheral human blood lymphocytes might express D3, D4, and D5 receptors (Ricci and Amenta, 1994; Ricci et al., 1995, 1997, 1998). Although DA receptor agonists have been reported to modulate some immune parameters, such as antibody response, T cell proliferation, and cytokine production (Pierpaoli and Maestroni, 1978; Hasko et al., 1996a), the functional role of DA in immunomodulation remains poorly understood. Nevertheless, it was found that DA taken up from the circulation by noradrenergic varicosities is released from there and may influence the cytokine production (Bencsics et al., 1997b). Furthermore, the possibility remains that some of the in vivo effects of DA might be mediated through its inhibition of the release of anterior pituitary hormones, which, alternatively, may affect immune functions.

B. Signal Pathways and Molecular Aspects of Catecholamines Actions

Heterotrimeric G-proteins regulate the transduction of transmembrane signals from cell surface receptors to variety of intracellular effectors, such as adenylate cyclase (AC) and phospholipase C (PLC). G-proteins consist of three distinct classes of subunits, α, β, and γ; in general the effector specificity is conferred by the α-subunit. At least seventeen different α-subunit genes have been identified in mammals and these have been divided into four major subfamilies: G_s, G_i, G_q, and G_{12}. The G_s family contains G_s and G_{olf}; these α-subunits stimulate AC. The G_i family contains G_i, G_o, and G_z subunits, which can inhibit AC and modulate potassium and calcium channels. In addition, $\beta\gamma$-subunits of the $\alpha\beta\gamma$ complex of G_i proteins have been shown to regulate β-isoforms of PLC. It is important that the α-subunits of the G_q subfamily (G_q, G_{11}, G_{14}, G_{15}, and G_{16}) have also been shown to activate the β-isoforms of PLC. The role of G_{12} subfamily is less well characterized (cf. Wu et al., 1995; Grant et al., 1997).

1. Cyclic Adenosine 5′-Monophosphate. NE and epinephrine transduce their biological information through stimulation of ARs. ARs directly activate G-proteins that stimulate enzymes, such as AC and PLC to induce the production of second messengers, such as cyclic adenosine 5′-monophosphate (cAMP) or intracellular inositol 1,4,5-triphospate (IP_3), diacylglycerol (DAG), and Ca^{2+}, respectively. In general, the β-ARs couple to G_s protein to activate AC that increases intracellular cAMP; the α_2-ARs couple to the G_i proteins to inhibit AC and subsequently the formation of cAMP, and the α_1-ARs couple to the G_α subunits of the G_q class to activate PLC that increases IP_3 and DAG. Subsequent to the generation of these second messengers, cAMP activates protein kinase A (PKA), whereas DAG activates protein kinase C (PKC), and IP_3 mobilizes Ca^{2+} from intracellular stores. Ca^{2+} is further linked to the Ca^{2+}/calmodulin (Ca^{2+}/CaM) pathway.

Recent studies indicate that the selectivity in the interactions of the ARs with different G-proteins is rather promiscuous in certain systems. Thus, recent evidence indicates that $G_{\alpha 15}$ and $G_{\alpha 16}$ are expressed only in certain hematopoietic cells with particularly high expression in pre-B cell lines (Grant et al., 1997). Recently Wu et al. (1995) found that β_2-ARs can specifically couple to $G_{\alpha 15}$ and $G_{\alpha 16}$ and that in this cotransfection system, NE is able to mediate increased accumulation of inositol phosphates. Thus, NE and epinephrine via stimulation of β-ARs may not only activate AC but also PLC in some hematopoietic cells. This may also explain some of the β-AR-mediated effects in certain hemopoietic systems that previously could not be completely interpreted by increases in the levels of cAMP (see also below).

The amount of cAMP in cells is controlled, on the one hand by the activity of AC, which catalyzes the conversion of ATP to cAMP, and, on the other hand, by phosphodiesterase (PDE), which degrades cAMP. PDEs represent a large and diverse group of enzymes that catalyze the hydrolytic cleavage of cAMP's 3′ phosphoester bond to form the inactive 5′AMP. The mammalian PDEs fall into seven known classes, each the product of different gene or family of genes. PDE4 is the most abundant isoenzyme class found in monocytes and most other immune cells (Thompson et al., 1976; Manning et al., 1996). Resting monocytes express both mRNA and protein for PDE4A, PDE4B, and PDE4D (Manning et al., 1996). cAMP executes its effects through activation of the PKA; PKA comprises two isoenzymes, type I (PKA-I) and type II (PKA-II). PKA-I is predominantly associated with the plasma membrane, whereas PKA-II is primarily localized in the cytosol. PKA, PKC, and Ca^{2+}/CaM pathways transfer signals to the nucleus. It appears that the PKC and Ca^{2+}/CaM pathways are activated, for example, by antigens and mitogens that primarily activate signal transduction pathways for cytokine gene transcription, whereas the cAMP/PKA pathway acts as a modulator (see also below). Important nuclear transcription factors for the expression of many genes, including those of cytokines comprise the nuclear transcription factor κB (NF-κB), the nuclear factor of activated T cells (NF-AT), the cAMP-responsive-element binding protein (CREB) and activator protein 1 (AP-1). PKC, Ca^{2+}/CaM, and cAMP/PKA pathways modulate the activity of these transcription factors by regulating their phosphorylation status (Haraguchi et al., 1995a). Evidence has been obtained in immune cells that cAMP level is increased by activation of β_2 (Fedyk et al., 1996), H_2 (Khan et al., 1985) receptors, by PGE_2 (Phipps et al., 1991), and by A2 adenosine receptors (cf. Zidek, 1999). Activation of these receptors by catecholamines, histamine, PGE_2 and adenosine results in an inhibition of TNF-α and IL-12 and an increase of IL-10 production

(Elenkov et al., 1995, 1996, 1998; van der Pouw Kraan et al., 1995; Haskó et al., 1996b; Link et al., 2000).

Adenosine, an endogenous ligand is able to increase the cAMP level and IL-10 production (Haskó et al., 1996b). In addition, adenosine and CGS-21680 HCl, a more selective A_{2a} than A_{2b} receptor agonist inhibited the lipopolysaccharide (LPS)-induced TNF-α serum level (Haskó et al., 1996b; cf. Zidek, 1999).

Immune cells contain type IV and type III PDE, the PDE IV type being prevalent in human mononuclear cells (cf. Zidek, 1999). The finding that amrirone, a selective PDE III, rolipram, a PDE IV, and theophylline, a nonselective PDE inhibitor prevent LPS to increase IL-12, TNF-α, IFN-γ, and NO production (Haskó et al., 1998 days; Németh et al., 1997a) also indicates that cAMP level plays an important role in the production of proinflammatory cytokines (Renz et al., 1988; Kambayashi et al., 1995; Souness et al., 1996). Since PDE inhibitors were able to inhibit proinflammatory cytokines also in IL-10 deficient mice (Haskó et al., 1998 days), it seems likely that this effect is independent of its action to enhance IL-10 production.

Induction of IL-2 promoter activity depends on a region adjacent to the transcription initiation site. This region contains the binding site for NF-κB, NF-AT, and AP-1 (cf. Tsuruta et al., 1995; Paliogianni and Boumpas, 1996). Elevated levels of cAMP are known to inhibit activation of NF-κB. The subunits that constitute NF-κB binding activity are members of the Rel family, which includes p50 and p65. In many cells, including monocytes and lymphocytes, NF-κB/Rel complexes are retained in the cytoplasm by the binding of the inhibitor protein IκB-α. The action of LPS or binding of an antigen to the CD3/TCR complex through calcineurin (CaN) and Ca^{2+}/CaM-dependent serine/threonine protein phosphatase induce the phosphorylation and proteolytic degradation of the inhibitory molecule of NF-κB, IκB-α, which allows the NF-κB/Rel complexes to translocate to the nucleus and induce expression of target genes, such as TNF-α and IL-2 (cf. Haraguchi et al., 1995a; Parry and Mackman, 1997). Kang et al. (1992) proposed that the p50/p65 heterodimer stimulates transcription, whereas the p50/p50 homodimer inhibits transcription of the IL-2 gene. The cAMP/PKA pathway, which induces impaired nuclear translocation and DNA binding of p65, probably due to a retarded degradation of IκB-α, antagonizes CaN-regulated cascades that stimulate transcription of the IL-2 gene (Neumann et al., 1995). The binding of the NF-κB (p50/p65) heterodimer to the NF-κB site is also inhibited by cAMP (Tsuruta et al., 1995). Furthermore, the activation of PKA pathway by cAMP inhibits NF-κB transcription by phosphorylating CREB, which competes with p65 for limited amounts of the transcriptional coactivator CREB-binding protein (Parry and Mackman, 1997). An important observation is that the NF-κB site is missing in the 5′ regulatory region of mouse IL-4 and human IL-10 genes, whereas IL-2 and TNF-α genes contain such sites (Chen and Rothenberg, 1994; Neumann et al., 1995; Platzer et al., 1995).

Cyclic AMP increasing agents down-regulate the activation of the IL-2 promoter also by modulating the AP-1 and NF-AT transactivating pathways required for its activation. In contrast to IL-2, an increase in cAMP does not affect IL-4 promoter activation (Paliogianni and Boumpas, 1996). It is conceivable that CREB could compete with AP-1 for binding at the AP-1 site, thus displacing it. This mechanism seems to be even more likely in view of the findings that cAMP also inhibited the binding of NF-AT, a nuclear factor that contains AP-1 protein (Paliogianni and Boumpas, 1996). Thus, AP-1 may be a prime target of cAMP in mediating its transcriptional effects on the IL-2 promoter. Through the above mechanisms, CA-induced increases in cAMP may inhibit the transcription of IL-2, TNF-α, and probably IL-12 genes.

CREB, a substrate of PKA, binds to and activates an enhancer containing the cAMP-responsive element (CRE) consensus sequence following elevation of cAMP. The cAMP stimulation of CRE-mediated gene transcription depends not only on the activity of protein kinases phosphorylating CREB but also on the Ca^{2+}/calmodulin-dependent protein phosphatase calcineurin that is necessary for the transcriptional competence of phosphorylated CREB (Schwaninger et al., 1995). Through this mechanism, cAMP may enhance IL-10 and IL-6 transcription through CRE in the regulatory region of the IL-10 and IL-6 genes (Platzer et al., 1995). Thus, both human and animal studies suggest that CAs, acting through the β_2-ARs-cAMP pathway, suppress type 1- but potentiate type 2-cytokine production and that this phenomenon also has molecular prerequisites (see *Section X.B.*).

2. Intracellular Ca^{2+}. It has been suggested that $[Ca^{2+}]_i$ plays an important role in the pathophysiology of endotoxemia and sepsis (Song et al., 1993; Hotchkiss et al., 1995). LPS has been shown to increase $[Ca^{2+}]_i$ in a variety of cells including macrophages (cf. Haskó et al., 1998e). Calcium channel blockers (verapamil, diltiazem) decrease the production of proinflammatory TNF-α (Hotchkiss et al., 1995; Szabó et al., 1997a) and IL-1α (Hotchkiss et al., 1995) but increases that of IL-10 (Szabó et al., 1997a). Dantrolene, a drug that inhibits the release of intracellular Ca^{2+} from its cytoplasmic stores suppresses plasma and tissue concentration of TNF-α (Haskó et al., 1998e), IL-1α, and IL-1β (Hotchkiss et al., 1995), increase plasma level of IL-10 and inhibits the production of IL-12 and IFN-γ in endotoxemic mice (Németh et al., 1998) and reduces $[Ca^{2+}]_i$ in macrophages (Haskó et al., 1998e). In this study, it was also shown that the effect of dantrolene to inhibit IL-12 production is independent of the presence of IL-10 in the plasma. In IL-10-deficient mice (C57BL/6), the IL-12 and IFN-γ responses to LPS were more than 70 and 3 times higher (Németh et al., 1998), but dantrolene was

still effective to inhibit their production without affecting the nuclear translocation of NF-κB (Haskó et al., 1998). Dantrolene is also able to prevent NO production by LPS (Haskó et al., 1998).

VII. Role of Sympathetic Innervation in Immune System Development and Hematopoiesis

A. Immune System Development

Clear distinction should be made between the role of SNS in immune system development and the effect of CAs on immune responsiveness (described under *Section X.*). At days 1 to 3 postnatally a few scattered fibers are present in the capsule and the septal system of the rat thymus and along the hilar vessels of the spleen. There is progressive growth into the parenchyma of these organs by postnatal day 7 when noradrenergic fibers begin to form a loose network. By postnatal day 14 in the rat the noradrenergic fibers increase in density, displaying both vascular and parenchymal patterns of innervation comparable with that seen in young adult thymus and spleen (Ackerman et al., 1987; Bellinger et al., 1987, 1988, 1992). At this age, NE concentration in the spleen also reaches adult levels (Ackerman et al., 1987).

With normal aging the thymus progressively degenerates and becomes infiltrated with adipose tissue. Noradrenergic innervation over the course of thymic involution does not decline, but rather persists, even though one of its presumed targets, thymocytes, are lost. With the shrinkage of this organ, noradrenergic nerve fibers are confined to a smaller volume of tissue, giving the appearance of hyperinnervation (Bellinger et al., 1992). Thus, unlike secondary lymphoid organs, the microenvironment of the aged thymus is capable of maintaining noradrenergic nerve fibers.

The adult pattern of nordrenergic innervation of the rat spleen persists through 12 months of age (Bellinger et al., 1987, 1992). At this time, a loss of T-lymphocytes in the periarteriolar lymphatic sheath, and a decline in the density of macrophages in the marginal zone, results in a reduced volume of the white pulp in which noradrenergic fibers reside. By 17 months of age, further loss of both T-lymphocytes and macrophages in the white pulp is apparent; however, at this time, a decline in the density of noradrenergic innervation is also observed. Progressive loss of noradrenergic innervation and the loss of T-lymphocytes and macrophages in the spleen continues throughout the lifespan of the aged. With the normal aging process, a decline in the T cell-mediated immune functions is well documented. Whether this phenomenon is causally linked to the decline in noradrenergic innervation of secondary lymphoid organs remains to be tested (Bellinger et al., 1992).

The early presence of noradrenergic innervation in specific compartments of the thymus and the spleen during critical periods of development points toward a role of NE in the maturation/development of the immune system and "shaping" of the immune responsiveness. This is substantiated by recent observations showing that neonatally sympathectomized rats express alterations in T and B cell proliferation and NK cell activity, the extent of which is influenced by gender and age (Ackerman et al., 1991; Madden et al., 1993). Neonatal sympathectomy also results in reduced immunoglobulin (Ig) M production throughout development (Ackerman et al., 1991).

B. Hematopoiesis

The bone marrow compartment contains the principal hematopoietic tissue and is the site of proliferation and maturation of multipotent stem cells into mature blood cells of different lineages. Murine bone marrow contains a substantial amount of CAs. NE and DA exhibit a daily rhythmicity, with peak values observed during the night. In addition, high and low values of NE and DA are associated with high and low values of their metabolites, whereas NE, but not DA or epinephrine, is positively associated with the proportion of cells in the G_2/M and S phases of the cell cycle (Maestroni et al., 1998). Thus, the SNS neural input of the bone marrow may be implicated in the regulation of hematopoiesis. Recently, Tang et al. (1999) demonstrated that cold exposure increased NE turnover rate in the murine bone marrow by 36%, whereas peritoneal *Pseudomonas aeruginosa* infection increased bone marrow NE turnover rate by 131%. Thus, environmental conditions and infectious agents known to elevate central sympathetic outflow induce local release of NE within the bone marrow. These findings also indicate that the noradrenergic innervation of the bone marrow is functionally dynamic and is responsive to generalized or immunological stress.

Administration of various doses of the α_1-AR antagonist prazosin were shown to increase the concentration of blood granulocytes and bone marrow granulocyte-macrophage colony forming units (GM-CFU) while decreasing the number of spleen B and T-lymphocytes (Maestroni et al., 1992; Maestroni and Conti, 1994b). These observations prompted Maestroni and Conti (1994a,b) to suggest that in vivo, myelopoiesis, and in particular the production of granulocytes and macrophages, are under a sympathetic inhibitory tone, whereas lymphocyte formation appears to need adrenergic stimulation. This is substantiated by the observations that α_1-ARs are present on bone marrow cells and NE inhibits the growth and differentiation of GM-CFU in vitro, a process mediated by α_1-ARs, and, to a lesser extend, by α_2-ARs (Maestroni and Conti, 1994a).

Stimulation of β-ARs might also participate in the modulatory effects of endogenous CAs in hematopoiesis (see also above, signal transduction). Mouse bone marrow contains a primitive pluripotent cell (stem cell), which following transplantation produces macroscopic colonies in the spleen of heavily irradiated mice; each

colony arises from a single cell. These cells are called colony forming units or CFU. In 1971, Byron (1971) demonstrated that upon exposure in vitro to low concentrations of isoproterenol, a β-AR agonist, resting mouse spleen CFUs begin to synthesize DNA as shown by increased sensitivity to the cytotoxic effects of both high specific activity [^{3}H]thymidine and hydroxyurea. These effects were blocked by propranolol, a β-AR antagonist. Hence, it was suggested that early progenitors in mice may be very sensitive to small amounts of CAs and that β-AR stimulation might serve to trigger hemopoietic stem cells into their cell cycle or to shorten their cell cycle (Byron, 1971). In animals, adrenergic agonists also stimulate erythropoiesis both in vivo (Fink and Fisher, 1977) and in vitro (Brown and Adamson, 1977). This appears to be also relevant to human erythropoiesis. Isoproterenol, when added to the culture over a wide range of concentrations, significantly enhanced human erythroid colony growth; this effect was mediated through β_2-ARs and required the presence of erythropoietin (Mladenovic and Adamson, 1984).

C. Thymocyte Development

Although the above discussed evidence that the thymic cortex (a site where immature thymocytes develop and differentiate to mature thymocytes or T lymphocytes) receives rich sympathetic innervation, our knowledge about the functional significance of these neural inputs is currently limited (see *Section IX.*). The cell surface glycoprotein Thy-1 expressed on immune cells and neurons of rodents and humans is hypothesized to function in cell adhesion and signal transduction in T cell differentiation and proliferation. Singh and Owen (1976) demonstrated that in culture, higher proportions of 14-day fetal thymus cells expressed Thy-1 and TL antigens following treatment with isoproterenol, an β-AR agonist; in contrast, a recent study demonstrated that isoproterenol caused concentration-dependent decreases in levels of Thy-1 mRNA in murine thymocytes, an effect prevented by the β-AR antagonist propranolol (Wajeman-Chao et al., 1998). Futhermore, organ cultures of 14-day fetal thymic explants treated with phenylephrine, an α_1-AR agonist, showed increased proliferative activity when assayed in terms of ^{125}I-UdR incorporation and cell yields, in comparison with untreated cultures (Singh, 1979).

Thymocytes mature and differentiate into T cells in the thymus under the influence of a microenvironment that is created by a number of supporting cells. TECs, secreting several cytokines as key factors of the thymic microenvironment, are supposed to be the major cell type involved. Recently von Patay et al. (1998, 1999) demonstrated that NE stimulated IL-6 production by TEC cultures about 14-fold over basal values after 24 h. IL-6 in combination with interferon-γ and IL-2 induces the differentiation of cytotoxic T cells from immature thymocytes (Takai et al., 1988), whereas IL-6 together with IL-2 or IL-4 enhances the proliferation of $CD4^+CD8^-$ or $CD4^+CD8^+$ single positive mouse thymocytes (Chen et al., 1989). Thus, NE may affect thymic development indirectly, through modulation of the secretion by TEC of key factors of the thymic microenvironment.

VIII. Sympathetic Control of Lymphocyte Traffic and Circulation

Lymphocyte migration, circulation, and traffic are under the influence of the CNS (for detailed reviews see Ottaway and Husband, 1992, 1994; Benschop et al., 1996) and the SNS plays a significant role in this process. Two phases are recognized after CA administration in humans: a quick (<30 min) mobilization of lymphocytes, followed by an increase of granulocytes with relative lymphopenia (maximal response at 2–4 h) (Benschop et al., 1996). CAs predominantly affect NK cells and granulocyte circulation, whereas T and B cell numbers remain relatively unaffected. Thus, infusion of both epinephrine and NE in humans induces a transient increase of total lymphocytes and numbers of $CD3^+$ and $CD8^+$ cells, and marked increases (between 400 and 600%) of NK cell numbers ($CD16^+$, $CD56^+$); two-color fluorescence analysis revealed that the changes in $CD8^+$ cells are mainly due to alterations in NK cells coexpressing CD8 rather than CD8+ T cells (Benschop et al., 1996; Schedlowski et al., 1996). Similarly, acute psychological stress or physical exercise induce a transient increase in lymphocyte numbers, in particular the NK cell number. The role of increased CA levels in this phenomenon has also been documented (cf. Benschop et al., 1996; Schedlowski et al., 1996). By contrast, a reduction of Tc and NK cells, without significant alteration of Th cells, were observed after 7 days of treatment with terbutaline, a β_2-AR selective agonist, changes identical to that seen in congestive heart failure patients (Maisel et al., 1990b). Thus, a short term, acute increase of sympathetic activity or a single infusion of adrenergic agents might have the opposite effect on NK cell numbers, than does prolonged sympathetic activity: in the short term, CAs acutely mobilize NK cells from depots, whereas in the long term, chronically, CAs decrease the number of lymphocytes, and particularly of NK cells in the peripheral blood. This is substantiated by the observation that in humans, the percentage of NK cells in peripheral blood in normal subjects is negatively correlated to plasma epinephrine levels (Knudsen et al., 1996).

CAs appear to modulate NK cell circulation via spleen-dependent and spleen-independent β_2-AR mechanisms: these changes are demonstrated to also occur in splenectomized subjects, suggesting that reservoirs other than the spleen, probably the marginating pool in blood vessels (the so-called marginal position of white blood cells in the venular system, see below) are also

utilized for this fast mobilization of lymphocytes, particularly NK cells (Schedlowski et al., 1996). Granulocyte increases, however, involve α-AR stimulation, and these cells are predominantly released from the marginal pool, the lung and the bone marrow (Benschop et al., 1996).

The mechanisms by which CAs modulate lymphocyte distribution are not well established. One possible mechanism is that the SNS, which directly innervates the vascular smooth muscle, regulates the regional blood flow, and thereby changes the delivery of lymphocytes to postcapillary venules of tissues, and the opportunity for lymphocytes to enter tissue. Perhaps the lymph flow is also under sympathetic control. Thus, electrical stimulation of regional sympathetic nerves results in increased lymphatic pumping, which in turn has marked effects on lymphocyte output, whereas application of α_1-adrenoreceptor agonists into the afferent lymphatics of sheep popliteal lymph nodes increases the output of lymphocytes in efferent lymph (cf. Ottaway and Husband, 1992, 1994).

As evident, different lymphocyte subpopulations have different sensitivity to CA effect on lymphocyte distribution; however, it remains unclear whether this is a direct effect, or indirectly mediated, through hemodynamic alterations. A direct effect might simply reflect, as discussed above, different expression and activity of β-ARs on lymphocyte subpopulations: although B cells have many β-ARs, they generate little cAMP in response to CAs, and CAs do not affect their circulating numbers; Th cells, which are only modestly affected by CAs, have substantially less β-ARs and generate only little cAMP in response to CAs compared with NK cells and Tc, which possess many more β-ARs and are mainly affected by CAs. In this respect, alterations in the adhesive interaction of NK lymphocytes are believed to be responsible for the release of NK cells from the marginating pool of blood vessels into the circulating population. In vitro evidence supports this view, since both epinephrine and NE through β_2-AR stimulation, cause detachment of NK cells from cultured endothelium (Benschop et al., 1993).

IX. Modulation of Lymphocyte Proliferation and K^+ Channel Conductance

Since selective K^+ channel blockers such as quinine and 4-aminopyridine inhibit IL-2 production and T cell proliferation, it was suggested that the modulation of K^+ channel conductance might be involved in control of the magnitude and extent of cellular activation and proliferation (DeCoursey et al., 1984; Premack and Gardner, 1991; Jensen et al., 1999). Thus, NE might be involved in the regulation of lymphocyte proliferation through modulation of K^+ channel gating.

Several lines of evidence suggest that CAs or β-AR agonists inhibit the T cell proliferation induced by mitogens (Hadden et al., 1970; Chambers et al., 1993). This is usually accompanied by an increase of cAMP in lymphocytes (Carlson et al., 1989a) and the amount of cAMP produced by T cells stimulated with isoproterenol, a β-AR agonist, is proportional to the degree of inhibition of the proliferation (Bartik et al., 1993). Binding of lymphocyte CD3/T cell receptor (TCR) complex to an antigen on the surface of an antigen-presenting cell (APC) triggers the process of T cell activation. This TCR-antigen interaction leads to the generation of intracellular signals that in turn orchestrate a complex series of events that lead to T cell proliferation and cytokine secretion. Importantly, as in the case of mitogens, a similar inhibitory effect of isoproterenol was also observed for the proliferative response of highly purified human T cells stimulated with immobilized anti-CD3 monoclonal antibody through the CD3/TCR complex (Elliott et al., 1992; Bartik et al., 1993). The proliferative response of $CD8^+$ T cells is inhibited to a greater extent than $CD4^+$ T cells, presumably because $CD8^+$ T cells have a higher number of β-ARs (Bartik et al., 1993). The elevation of cAMP also inhibits IL-2 secretion by T cells (Bartik et al., 1993), thus suggesting that the inhibition of T cell proliferation might be due, at least in part, to the inhibition of the production of IL-2, a cytokine that is an important costimulatory molecule in T cell proliferation. However, the antigen-stimulated T cell proliferation seems to be more sensitive to a rise in cAMP than the IL-2-induced T cell proliferation (Bartik et al., 1993).

Activation of human T lymphocytes via the CD3/TCR complex or by mitogens produces an enhanced turnover of phosphatidylinositol (PI) cycle-related phospholipids accompanied by the increased production of DAG and phosphorylated derivatives of inositol (IP). Stimulation through the CD2 molecule, which is considered as a CD3/TCR alternative or costimulatory antigen-independent pathway of T cell activation, triggers identical PI cycle-related metabolic events. Recently Bismuth et al. (1988) demonstrated that increased intracellular cAMP inhibited the enhanced turnover of PI cycle-related phospholipids induced by anti-CD2 monoclonal antibodies, and, in parallel, both the DAG production and the IP release were strongly reduced. These results indicate that the increase of intracellular cAMP might interfere at one or more levels of the PI cycle metabolic process triggered through antigen-dependent CD3/TCR complex or antigen-independent CD2 pathway.

A. T Lymphocytes Express a Plethora of Ion Channels

Using patch-clamp techniques, the presence of voltage-dependent potassium (K^+) channels (i.e., the opening rate of the channel increases with membrane depolarization) in murine and human lymphocytes has been shown (DeCoursey et al., 1984; Lewis and Cahalan, 1988; Jensen et al., 1999). Potassium channels play a critical role in the modulation of T cell calcium signaling and subsequent regulation of proliferation. They repre-

sent the predominant ion channels in T cells (Premack and Gardner, 1991).

We have demonstrated that NE is able to inhibit in a concentration-dependent manner the outward voltage-dependent K^+ currents recorded from rat thymocytes (Vizi et al., 1995). This effect is more pronounced at the end of the registered current, suggesting that NE may act predominantly through increasing the rate of inactivation of the voltage-dependent K^+ current. Similarly, in $CD8^+$ human peripheral lymphocytes, isoproterenol, a β-AR agonist, decreases the peak current amplitude and increases the rate of inactivation of the K^+ current (Soliven and Nelson, 1990). These effects were antagonized by the β-AR-blocker propranolol, whereas dibutyryl cAMP and cholera toxin mimicked the effect of isoproterenol. Thus, the modulatory effects of NE and β-AR agonists on voltage-dependent K^+ channel conductance appear to be receptor-mediated and could involve cAMP-dependent pathways as well as G-proteins.

Several lines of evidence indicate that K^+ channels are involved in the processes of lymphocyte activation, proliferation and differentiation. Thus, K^+ channels are expressed very early in T cell differentiation, possibly before thymic processing (Schlichter et al., 1986) and the expression of K^+ channels varies during mouse T cell development (McKinnon and Ceredig, 1986; Lewis and Cahalan, 1988; Ishida and Chused, 1993), while activation of T cells by mitogens and IL-2 up-regulates the expression of K^+ channels and amplifies the potassium conductance (cf. Premack and Gardner, 1991). It is interesting to note that progesterone at concentrations found in the placenta, rapidly and reversibly blocks voltage-gated and calcium-activated K^+ channels (Ehring et al., 1998). This effect contributes to progesterone-induced immunosuppression. Thus, NE might be involved in the regulation of lymphocyte proliferation through modulation of K^+ channel gating. Through the same mechanism, CAs might participate in the regulation of thymocyte or lymphocyte responsiveness to regulatory signals from blood-borne or locally released hormones and cytokines (Vizi et al., 1995).

X. Modulation of cellular and humoral immunity by catecholamines

A. T Helper 1/T Helper 2 Paradigm: Role of Type 1 and Type 2 Cytokines

Immune responses are regulated by APCs, such as monocytes/macrophages, dendritic cells, and other phagocytic cells, that are components of *innate immunity*, and by T helper (Th) lymphocyte subclasses Th1 and Th2, that are components of *acquired (adaptive) immunity*. Th1 cells primarily secrete IFN-γ, IL-2, and TNF-β, which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-10, IL-13 (Abbas et al., 1996; Fearon and Locksley, 1996; Mosmann and Sad, 1996), and IL-9 (Grohmann et al., 2000), which promote humoral immunity (Fig. 2).

Naive $CD4^+$ (antigen-inexperienced) Th0 cells are clearly bipotential and serve as precursors of Th1 and Th2 cells. Among the factors currently known to influence the differentiation of these cells toward Th1 or Th2, cytokines produced by cells of the innate immune system are the most important (Fearon and Locksley, 1996). Thus, IL-12, produced by activated monocytes/macrophages or other APCs, is a major inducer of Th1 differentiation and hence cellular immunity; this cytokine acts in concert with NK-derived IFN-γ to further promote Th1 responses (Trinchieri, 1995). APC-derived IL-12 and TNF-α in concert with natural killer (NK) cell- and Th1 cell-derived IFN-γ stimulate the functional activity of Tc, NK cells, and activated macrophages, i.e., the major components of cellular immunity. All three cytokines, IL-12, TNF-α and IFN-γ, also stimulate the synthesis of NO and other inflammatory mediators that drive chronic delayed type inflammatory responses. Because of these crucial and synergistic roles in inflammation IL-12, TNF-α, and IFN-γ are considered the major pro-inflammatory cytokines (Trinchieri, 1995; Fearon and Locksley, 1996; Mosmann and Sad, 1996).

Th1 and Th2 responses are mutually inhibitory (Fig. 2). Thus, IL-12 and IFN-γ inhibit Th2, and vice versa, IL-4 and IL-10 inhibit Th1 responses. IL-4 and IL-10 promote humoral immunity by stimulating the growth and activation of mast cells and eosinophils, the differentiation of B cells into antibody-secreting B cells, and B cell immunoglobulin switching to IgE. Of importance, these cytokines inhibit macrophage activation, T cell proliferation and the production of pro-inflammatory cytokines (Abbas et al., 1996; Fearon and Locksley, 1996; Mosmann and Sad, 1996). Thus, IL-4 and IL-10 are the major anti-inflammatory cytokines.

B. Effects of Catecholamines and Drugs (α_2- and β_2-Adrenoreceptor Agonists and Antagonists, Phosphodiesterase Type IV Inhibitors) on the Production of Type 1 and Type 2 Cytokines

An increasing body of evidence suggests that CAs inhibit selectively Th1 functions, and favor Th2 responses, rather than causing generalized immunosuppression, as previously believed. CAs appear to suppress Th1 activities and cellular immunity and to boost Th2 and humoral responses at the level of APCs and Th1 cells, or act directly on the cellular components of both cellular and humoral immunity (Fig. 2). The effect of CAs on the production of different cytokines is summarized in Table 4.

1. Effect on Antigen-Presenting Cells. We recently demonstrated that both NE and epinephrine potently inhibited the production of the main inducer of Th1 responses, IL-12, in human whole blood cultures stimulated with bacterial LPS ex vivo (Elenkov et al., 1996). These effects were mediated by stimulation of β-ARs on

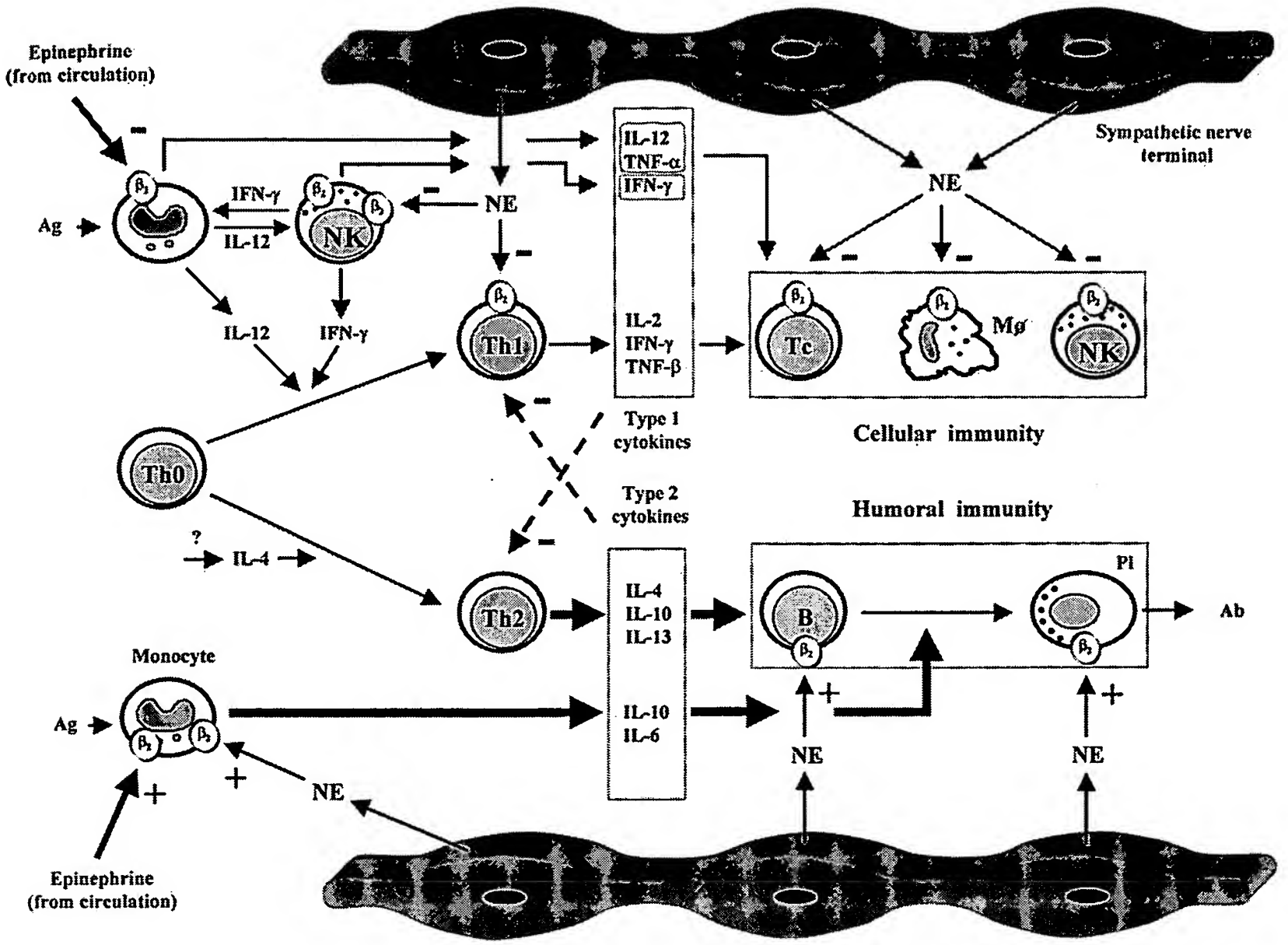

FIG. 2. Role of Th1 and Th2 cells, and type 1 (pro-inflammatory) and type 2 (anti-inflammatory) cytokines in the regulation of cellular and humoral immunity. Cellular immunity is stimulated by type 1 cytokines, secreted by APCs and Th1 cells, whereas humoral immunity is stimulated by type 2 cytokines secreted by APCs and Th2 cells. The cellular source of IL-4 that stimulates the Th0 to Th2 differentiation is not well defined. Cellular immunity provides protection against intracellular bacteria, protozoa, fungi, and several viruses, whereas humoral immunity provides protection against multicellular parasites, extracellular bacteria, some viruses, soluble toxins, and allergens. Systemic, Th2-driving effects of NE released from the postganglionic sympathetic nerve terminals in blood vessels and lymphoid organs, and of epinephrine, secreted from the adrenal medulla on the production of key regulatory type 1 and type 2 cytokines, Th1 and Th2 functions and, respectively, components of cellular and humoral immunity. Solid lines, stimulation; dashed lines, inhibition. Ag, antigen; T, T cell; B, B cell; Pl, plasma cell; Mø, macrophage.

monocytes, and epinephrine appears to be a strong inhibitor of IL-12 production, exhibiting an EC_{50} of 10^{-9} M. More recently, nonselective β- and selective β_2-AR agonists were shown to inhibit the production of IL-12 by monocytes and dendritic cells in both in vitro and in vivo conditions (Panina-Bordignon et al., 1997; Hasko et al., 1998a). Since IL-12 is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis by T cells, the inhibition of IL-12 production may represent one of the major mechanisms by which CAs affect the Th1/Th2 balance. Thus, in conjunction with their ability to suppress IL-12 production, β_2-AR agonists inhibited the development of Th1-type cells, while promoting Th2 cell differentiation (Panina-Bordignon et al., 1997). TNF-α is another major pro-inflammatory cytokine that in concert with IL-12 plays a central pathogenic role in several type 1-driven autoimmune reactions. Several lines of evidence suggest that NE, epinephrine, and β-AR agonists inhibit the production of TNF-α by LPS-treated monocytes, microglial cells, and astrocytes (Hetier et al., 1991; Severn et al., 1992; van der Poll et al., 1994; Nakamura et al., 1998) and by human mast cells stimulated with IgE (Bissonnette and Befus, 1997). Increased extraneuronal concentration of CAs resulting from inhibition of their reuptake by desipramine was also recently associated with decreased neuronal-associated TNF-α immunoreactivity in rat hippocampus and locus ceruleus (Ignatowski et al., 1997). CAs also suppress the production of IL-1 (Koff et al., 1986), another pro-inflammatory cytokine, an effect that is mostly indirect via inhibition of TNF-α and potentiation of IL-10 production (van der Poll and Lowry, 1997a).

While suppressing type 1 cytokine production, CAs appear to up-regulate the production of type 2 cytokines by APCs (Fig. 2). Thus, the production of IL-10, one of the most potent anti-inflammatory cytokines induced by LPS in human monocytes or mouse peritoneal macrophages, is potentiated by NE, epinephrine, and β_2-AR agonists, an effect that is β_2-AR-mediated and cAMP-PKA-dependent (Elenkov et al., 1996; van der Poll et al.,

TABLE 4
β-ARs-mediated effects of CAs on cytokine and chemokine production

Cytokine	Type	Source	Effect	Comments	References
IL-12	Type 1, pro-inflammatory	APCs	↓	Major inducer of Th1 responses	Elenkov et al., 1996; Panina-Bordignon et al., 1997; Hasko et al., 1998c,d
TNF-α	Type 1, pro-inflammatory	APCs	↓[a]	Major pro-inflammatory cytokine	Severn et al., 1992; Elenkov et al., 1995; Hasko et al., 1995a
IFN-γ	Type 1, pro-inflammatory	Th1 cells, NK cells	↓	Potent activator of macrophages and inhibitor of Th2 functions	Sanders et al., 1997; Borger et al., 1998
IL-2	Type 1	Th0, Th1 cells, NK cells	↓	Important proliferative factor for lymphocytes	Chouaib et al., 1985
IL-1	Pro-inflammatory	APCs, fibroblasts, endothelium, many other cells	↓[a]	Major pro-inflammatory cytokine; endogeneous pyrogen	Koff et al., 1986b; van der Poll and Lowry, 1997a
IL-4	Type 2, anti-inflammatory	Th2 cells	No effect[b]	β-ARs are not expressed on Th2 cells	Sanders et al., 1997; Borger et al., 1998
IL-10	Type 2, anti-inflammatory	APCs, Th2 cells	↑ (APCs)[b]	Potent inhibitor of Th1 and macrophage functions	Elenkov et al., 1996; van der Poll et al., 1996; Suberville et al., 1996b
IL-6	Type 2 (?), pro- and anti-inflammatory	APCs, Th2 cells, TEC	↑ (APCs)[b]	BCDF, inducer of acute phase proteins	DeRijk et al., 1994; Hasko et al., 1995a; Papanicolaou et al., 1996
TGF-β	Type 2, anti-inflammatory	Wide variety of cells	↑ (fibroblasts)	Potent inhibitor of Th1 and macrophage functions	Fisher and Absher, 1995
IL-8	Pro-inflammatory	Monocytes endothelium	↑	Chemotactic for neutrophils	Linden, 1996; van der Poll and Lowry, 1997b
IL-3	Hemopoietic factor	T cells	↓	Pan-specific colony-stimulating factor	Borger et al., 1996
GM-CSF	Hemopoietic factor	Lymphocytes	↓	Promotes the development of the precursors of granulocytes and macrophages	Borger et al., 1996
MIP-1α	Pro-inflammatory	Lymphocytes	↓	Chemotactic for macrophages and T lymphocytes	Hasko et al., 1998b

[a] See also local responses and macrophage functions.
[b] CAs are probably not able to affect the production of type 2 cytokines by Th2 cells directly, simply because they do not express β-ARs. Indirectly, however, they may potentiate the cytokine production by Th2, since they remove the inhibitory restraints on these cells exerted mainly by IL-12 and IFN-γ.

1996; Suberville et al., 1996; Siegmund et al., 1998). Similarly, the production of IL-6, a cytokine that exerts both pro- and anti-inflammatory effects, but possesses mostly Th2-type activities (previously known as BCDF, B cell differentiation factor) is also up-regulated by CAs. Thus, the production of IL-6 from astrocytes, but not microglia, was recently shown to be potentiated by CAs, an effect due to stimulation of the β-AR-cAMP pathway (Maimone et al., 1993; Norris and Benveniste, 1993). Interestingly, stimulation of β_2-ARs by NE was reported to stimulate IL-6 production by TEC cultures about a 14-fold over basal values (von Patay et al., 1998, 1999), whereas NE induced about 40-fold increase of IL-6 production in mouse brown adipocytes, an effect through the β_3-ARs (Burysek and Houstek, 1997). Furthermore, another catecholamine, DA, appears to increase the release of IL-6 from rat adrenal zona glomerulosa cells (Ritchie et al., 1996).

2. *Effect on T Helper 1 Cells.* Although Mohede et al. (1996) have shown that β-AR agonists inhibit IL-4 production by human PBMC, more recent studies suggest that CAs do not affect directly Th2 cells cytokine production and functions. The finding that β_2-ARs are expressed on Th1 cells, but not on Th2 cells (Sanders et al., 1997) provides a mechanistic basis for the differential effect of CAs on Th1/Th2 functions. Of importance, in both murine and human systems, β_2-AR agonists inhibit IFN-γ production by Th1 cells, but do not affect IL-4 production by Th2 cells (Sanders et al., 1997; Borger et al., 1998). Furthermore, cAMP levels increase in Th1 cells following terbutaline exposure, but not in Th2 cells, even though AC is present and functional in both Th subsets (Sanders et al., 1997). IFN-γ-producing Th1 cells induce B cells to produce IgG2a (in humans, IgG1), whereas IL-4-producing Th2 cells induce B cells to produce IgE and IgG1 (in humans, IgG4) (Fearon and Locksley, 1996). Thus, in the study of Sanders et al. (1997) the inhibition of IFN-γ production by Th1 cells induced by the β_2-AR agonist terbutaline was associated with subsequent suppressed IgG2a production by mouse B

cells, whereas the lack of effect on IL-4 was associated with no changes in IgG1 production by B cells. In addition, isoproterenol, or other agents that activate the cAMP-PKA pathway, were reported to inhibit IL-2 production by T cells and to down-regulate their IL-2 and transferrin receptor expression (Chouaib et al., 1985; Feldman et al., 1987; Mary et al., 1987; Anastassiou et al., 1992).

3. In Vivo Effects. It is important to note that the differential effect of CAs on type1/type2 cytokine production also operates in in vivo conditions. Thus, increasing sympathetic outflow and endogenous production of CAs in mice by selective α_2-AR antagonists, or application of exogenous CAs or β-AR agonists results in inhibition of LPS-induced TNF-α (Elenkov et al., 1995; Szelényi et al., 2000a,b) and IL-12 production (Elenkov et al., 1995; Hasko et al., 1998d). Catecholamines also appear to exert tonic inhibition on the production of pro-inflammatory cytokines in vivo. Thus, application of propranolol, a β-AR antagonist that blocks their inhibitory effect on cytokine-producing cells, results in substantial increases of LPS-induced secretion of TNF-α (Elenkov et al., 1995) and IL-12 in mice (Elenkov et al., 1995; Hasko et al., 1998d,e), whereas, in IL-10 deficient C57BL/6 IL-10 (−/−) mice, plasma levels of IL-12 were about 70-fold higher than in their counterparts, suggesting tonic inhibitory effect of IL-10 on IL-12 production. Injection of isoproterenol, although augmenting the IL-10 response in C57BL/6 IL-10 (+/+) mice, inhibited IL-12 production in both C57BL/6 IL-10 (+/+) and C57BL/6 IL-10 (−/−) mice (Hasko et al., 1998d). Thus, the inhibition of IL-12 production appears to be independent of the increased release of IL-10. In humans, the administration of the β_2-AR agonist salbutamol results in inhibition of IL-12 production ex vivo (Panina-Bordignon et al., 1997), whereas acute brain trauma that is followed by massive release of CAs triggers secretion of substantial amounts of systemic IL-10 (Woiciechowsky et al., 1998). Phosphodiesterase type IV inhibitors that increase intracellular cAMP in lymphoid cells suppress, both in vitro and in vivo, the production of type 1 cytokines such as IL-12, TNF-α, and IFN-γ, whereas they up-regulate the production of IL-10, a type 2 cytokine (see *Section XIV.*). Furthermore, in animals or humans, exogenous CAs increased sympathetic outflow and endogenous production of CAs by selective α_2-AR antagonists, excessive exercise, immobilization stress, or elective craniotomy via a β-AR-mediated pathway that potentiates the production of IL-6 in in vivo conditions (DeRijk et al., 1994; Takaki et al., 1994; Hasko et al., 1995a; Heesen et al., 1996; Papanicolaou et al., 1996).

Of importance, in mice, pretreatment with salbutamol also induces an increase of the ex vivo release of IL-4, IL-6, and IL-10 from concanavalin A-activated splenocytes (Coqueret et al., 1994a). This might have resulted from the reversal of the suppressive effects of IL-12 and IFN-γ on the production of cytokines by Th2 cells. Thus, it appears that CAs do not have a direct effect on the secretion of cytokines from Th2 cells but inhibit the production of type 1 cytokines by both APCs and Th1 cells, although potentiating the production of type 2 cytokines by APC. In vivo, however, when both APCs and Th1 and Th2 cells are present, the overall effect of CAs might be inhibition of type 1 secretion by APCs and Th1 cells with concomitant potentiation of IL-10 and IL-6 production by APCs. In parallel, the production of the type 2 cytokine by Th2 cells is also potentiated, due to the removal of the inhibition by type 1 cytokines on these cells (Fig. 2, Table 4).

4. Local Responses. The above-mentioned evidence, obtained from both human and animal studies, indicates that systemically, CAs inhibit type 1 but stimulate type 2 cytokine secretion, respectively. In local responses, in specific compartments, the effect of CAs may be different. Thus, NE, via stimulation of α_2-ARs, can augment LPS-stimulated production of TNF-α from mouse peritoneal macrophages (Spengler et al., 1990), whereas experimental hemorrhage in mice, a condition associated with elevations of systemic CA concentration, increases the expression of TNF-α and IL-1 by lung mononuclear cells through stimulation of α-AR (Le Tulzo et al., 1997). Since the response to β-AR agonist stimulation wanes during maturation of the human monocyte to a macrophage (Baker and Fuller, 1995), it is possible that in certain compartments of the body, the α-AR-mediated effect of CA becomes transiently dominant. Through this mechanism, CAs may actually boost local cellular immune responses in a transitory fashion. This is further substantiated by the finding that CAs, through stimulation of β_2-ARs potentiate the production of IL-8 from human monocytes and epithelial cells of the lung (Linden, 1996; van der Poll and Lowry, 1997b), thus probably promoting recruitment of polymorphonuclear leukocytes to this organ (see Table 4). Thus, in summary, whereas CAs suppress Th1 responses and pro-inflammatory cytokine secretion and boost Th2 responses systemically, they may differ in how they affect certain local responses. The possible mechanisms that determine the difference between systemic and certain local effects of CAs are discussed in details below (see *Section X.D.2.*).

C. Effect of Catecholamines on Chemokine Production

The recruitment of T cells, macrophages, and polymorphonuclear cells to an inflammatory site is greatly enhanced by the action of chemotactic cytokines termed chemokines, a large family of secreted 8- to 10-kDa proteins. In general, chemokines of the CXC subfamily or α-chemokines, such as IL-8, are specific in recruiting neutrophils and, to varying extents, lymphocytes, whereas chemokines from the CC subfamily or β-chemokines such as MCP (MCP-1, MCP-2, and MCP-3, monocyte chemotactic protein) and MIP (MIP-1α and MIP-1β, macrophage inflammatory protein) are chemotactic for monocytes and variably for NK cells, basophils, and eosinophils. The

β-chemokine eotaxin is highly specific for eosinophils, and the presence of significant concentrations of this mediator together with RANTES (regulated upon activation normal T cell expressed and secreted) in mucosal surfaces could account for the enhanced population of eosinophils in those tissues. Thus, the system of chemokines might serve to focus the immune defenses around the invading microorganisms.

Interleukin-8, produced by monocytes, macrophages, and endothelial cells, is a major factor in neutrophil-mediated inflammation, by activating and recruiting neutrophils into inflamed tissue compartments. IL-8 also induces expression of surface adhesion molecules, production of reactive oxygen metabolites, and degranulation. As mentioned above, CAs, through β-AR-mediated mechanisms, potentiate the production of IL-8 from LPS-stimulated monocytes and epithelial cells of the lung (Linden, 1996; van der Poll and Lowry, 1997b). Recent evidence suggests that epinephrine might promote IL-8 production in human leukocytes via an effect on platelets. Thus, IL-8 levels in samples containing platelets and stimulated with LPS and epinephrine were significantly higher than control samples containing no platelets (Engstad et al., 1999). In fact, as shown by Kaplanski et al. (1993) activated platelets are able to induce endothelial secretion of IL-8. These observations may provide a novel relationship between coagulation, Cas, and inflammation. Interestingly, IL-8 was also suggested to be a mediator of sympathetic pain; IL-8 evoked hyperalgesia in a rat paw pressure test by a prostaglandin-independent mechanism (Cunha et al., 1991). Thus, IL-8 might be the first endogenous mediator to be identified as evoking hyperalgesia involving the SNS.

The CC-chemokine MIP-1α is produced by a number of cells including neutrophils, activated lymphocytes, and fibroblasts. MIP-1α is chemotactic for leukocytes, monocytes/macrophages, and T lymphocytes, particularly $CD8^+$ T cells. In addition, it potently activates macrophages to secrete TNF-α, IL-1, and IL-6. MIP-1α appears to contribute to lung leukocyte recruitment and capillary leak age, the early mortality in endotoxemia, and the pathogenesis of rheumatoid arthritis. Recently Hasko et al. (1998b) demonstrated that exogenous and endogenous CAs inhibit the production of MIP-1α via a β-AR-mediated mechanism. Thus, CAs are probably important endogenous regulators of MIP-1α expression in inflammation. The overall effect of SNS on the chemokine system, however, as well as the effect of CAs on the production of the other members of chemokine α- and β-subfamily, is currently not understood.

D. Effects of Catecholamines and Drugs on the Cellular Components of Immunity

1. Natural Killer Cell Activity. CAs appear to have a dual effect on NK cells. On one hand, CAs (mostly epinephrine) mediate an acute, short lasting, and transient increase of NK cells numbers due to their mobilization from depots (see text above); on the other hand, however, CAs appear to mediate, both acutely and chronically, an inhibition of NK cell activity. This is substantiated by several in vitro and in vivo studies. Thus, application of epinephrine and isoproterenol in vitro elevates cAMP about 2.5-fold and induces an inhibition of NK cell activity (Hellstrand and Hermodsson, 1989; Whalen and Bankhurst, 1990). This effect is blocked by propranolol and mimicked by terbutaline, a β2-AR agonist, indicating the involvement of β2-ARs in this process (Hellstrand and Hermodsson, 1989; Whalen and Bankhurst, 1990).

In vivo, administration of the β2-AR agonist metaproterenol in Fischer (F344) rats suppresses blood NK activity in a dose-dependent manner (Shakhar and Ben-Eliyahu, 1998), whereas stimulation of the splenic nerve in Wistar rats results also in suppression of NK activity, an effect that is completely blocked by nadolol, a peripherally acting β-AR antagonist (Katafuchi et al., 1993). Furthermore, central administration of CRH, which is known to increase the sympathetic autonomic outflow, is accompanied by decreased NK activity in the periphery (Irwin et al., 1992; Strausbaugh and Irwin, 1992; Irwin, 1994). This effect is independent of the adrenocortical activation, since chlorisondamine, a ganglionic blocker of the peripheral sympathetic neurotransmission, or propranolol, a β-AR antagonist, prevent the CRH-induced inhibition of NK activity. The effect of central CRH is rapid; within 20 min of the infusion, lytic values of splenic NK cells decline by nearly 50%, whereas the cytotoxicity of peripheral NK cells is reduced within 1 h (Strausbaugh and Irwin, 1992; Irwin, 1994). In patients with heart failure, a disease characterized by chronically high levels of plasma NE, these levels correlate with anergy in the cytotoxicity of circulating NK cells and with their response to the stimulation with IL-2 and IFN-γ (Vredevoe et al., 1995).

Moreover, several lines of evidence suggest that stress, which is accompanied by increased levels of peripheral CAs, inhibits several components of cellular immunity and particularly NK cell activity, an effect that is mediated mainly by the CRH-SNS axis (Irwin, 1994) (see also text above and below). Thus, in animals, the application of anti-CRH antibodies completely blocks the inhibitory effect of footshock stress on NK activity (Irwin, 1994). It appears that NK cells are the most "sensitive" cells to the suppressive effect of stress, and not surprisingly, NK cell activity has become a bona fide index of stress-induced suppression of cellular immunity, employed in many studies (for review see Irwin, 1994). Interestingly, the serum levels of the sympathetic cotransmitter NPY are increased in patients with major depression and in persons undergoing severe Alzheimer caregiver stress and correlate inversely with NK activity. This is in accord with the above-mentioned direct inhibitory effect of NPY, in vitro, on human NK cell activity (Nair et al., 1993).

The potent suppressive effect of CAs on NK cell activity is probably due to the above-discussed fact that NK cells probably possess the highest number of β_2-ARs among lymphoid cells. Apart from this direct and acute effect, chronically, for example during subacute or chronic stress, CAs may suppress NK activity indirectly, through their selective suppression of Th1-type cytokines, and particularly through the above-discussed potent inhibition of the production of IL-12 and IFN-γ, cytokines essential for NK activity.

2. Macrophage Activity. Peripheral, circulating monocytes after activation and/or migration to a particular organ differentiate into macrophages. Although peripheral monocytes appear to express only the β-ARs and the effect of CAs on their function and cytokine production appear to be more clear-cut (see above), the effect of CAs on macrophage functions appears to be more complex (see Fig. 3) and the subject of some controversies.

Epinephrine and NE block the capacity of IFN-γ to activate murine macrophages to a tumoricidal state as measured by the lysis of ^{125}I-UdR-labeled melanoma target cells, or to a cytotoxic state capable of selectively killing herpes simplex virus-infected cells (Koff and Dunegan, 1985, 1986). However, both NE and epinephrine stimulate resident peritoneal macrophages from BALB/c mice to suppress the growth of *Mycobacterium avium*, an effect mediated by α_2-ARs (Miles et al., 1996). This is in accord with the already mentioned study of Spengler et al. (1990b) showing an α_2-AR-mediated stimulatory effect of NE on the production of TNF-α by mouse peritoneal macrophages. In apparent contrast, Bermudez et al. (1990) observed that treatment with epinephrine decreased the ability of human monocyte-derived macrophages to kill *M. avium*, although Miles et al. (1996) did not observe any increase in TNF-α production by resident murine peritoneal macrophages as a result of CA stimulation.

Furthermore, several studies demonstrate that in both mouse and rat peritoneal macrophages or macrophage cell lines CAs, β-AR agonists, and cyclic AMP accumulation inhibit TNF-α and IL-1 and potentiate IL-10 production (Koff et al., 1986; Chou et al., 1996; Suberville et al., 1996; Hasko et al., 1998a; Németh et al., 1997b). The apparent discrepancy between stimulatory and inhibitory activities of CAs may be attributed to the state of activation of macrophage populations: antigen challenge and activation of macrophages may result in an increase in β receptors and suppression of the response. It is highly likely, however, that there is a transient stage of differentiation when human monocytes (during maturation to macrophages) lose their β-AR responsiveness (see Baker and Fuller, 1995). Thus, naïve cells may preferentially express α-AR, which will result in stimulation of macrophage activity.

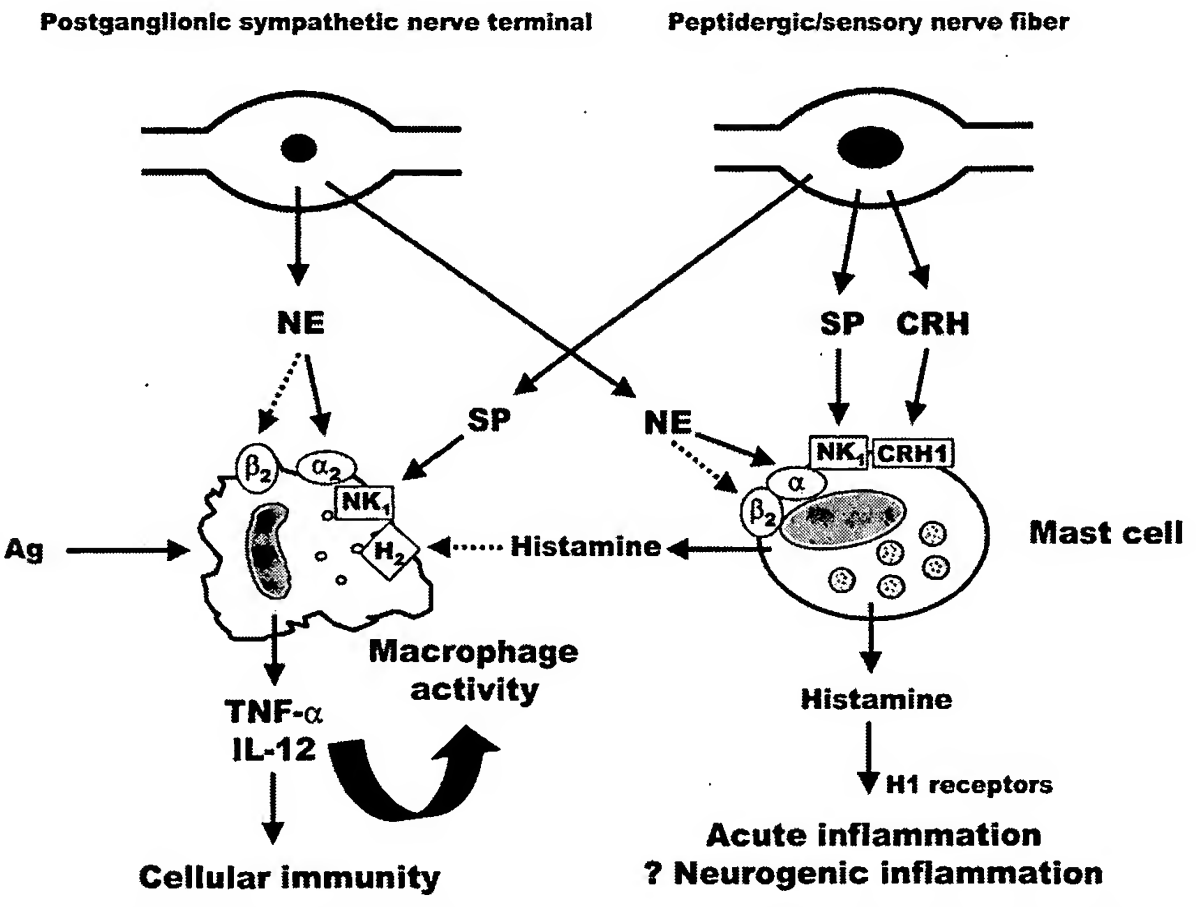

FIG. 3. Simplified scheme of the effect of locally released mediators on the secretion of TNF-α and IL-12, and macrophage activity. TNF-α and IL-12 stimulate the activity of activated macrophages, NK cells, and Tc, the major component of cellular immunity. Excessive production of TNF-α and IL-12 play a key role in the inflammatory activity and the tissue damage observed in organ-specific autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. Apart from the modulatory effects of NE through β_2- and α_2-adrenoreceptors (the β_2-adrenoreceptor-mediated inhibitory effect is most likely the dominant one; see text), macrophage activity might me affected by locally secreted SP by peptidergic/sensory nerve fibers or histamine, secreted by mast cells. Note that the release of SP and CRH may trigger the secretion of histamine, which, in turn, mediates vasodilatation, acute inflammation, or neurogenic inflammation through stimulation of H1 histamine receptors. Thus, the "anti-inflammatory effect", in general, of catecholamines exerted through stimulation of β_2-adrenoreceptors depends on the presence and expression of α-adrenoreceptors on macrophages and mast cells, and other local mediators or factors (see text for details).

In fact, the α_2-AR-mediated stimulatory effects of NE on TNF-α production was observed in peritoneal macrophages elicited from specific pathogen-free mice (Spengler et al., 1990), a condition that may reflect naïve, antigen-inexperienced macrophages. Furthermore, recent studies suggest that the β-AR responsiveness of rat peritoneal macrophages is a dynamic process (Chou et al., 1996; Ignatowski et al., 1996). Thus, minimal responsiveness to isoproterenol, β-AR agonist, was observed with resident macrophages; maximum isoproterenol-induced inhibition of TNF-α production was observed with complete Freund's adjuvant-elicited macrophages and significantly less with macrophages from streptococcal cell wall-injected rats (Chou et al., 1996). Most of the above-mentioned studies have been done in rodents, or they reflect in vitro conditions using murine macrophages. Further studies are needed to address the question whether these differences are relevant for human macrophage functions.

As already mentioned (see *Section III.*; Fig. 3), anatomically, a close spatial relationship between sympathetic and peptidergic nerve fibers on one hand, and macrophages and mast cells on the other hand, is frequently observed. Neuromacrophage and neuromast cell connections are not restricted to the preformed lymphoid organs and tissues, but are also regularly encountered in virtually all somatic and visceral tissues. SP and peripheral CRH, which are released from sensory peptidergic neurons, are one of the most potent mast cell secretagogues (Foreman, 1987; Church et al., 1991; Theoharides et al., 1995; Theoharides et al., 1998). Furthermore, recent evidence indicates that SP potentiates both TNF-α and IL-12 production by human and murine monocytes and macrophages (Lotz et al., 1988; Kincy-Cain and Bost, 1997; Ho et al., 1998). As mentioned previously, CAs, through stimulation of α- and β_2-adrenoreceptors, stimulate and inhibit, respectively, the release of histamine from mast cells, whereas histamine, through stimulation of H2 histamine receptors suppress the production of TNF-α and IL-12 production (Kaliner et al., 1972; Tomita et al., 1974; Elenkov et al., 1998).

The membrane-bound costimulatory molecules of the B7 family expressed on antigen-presenting cells are important for T cell activation. Recent evidence indicates that cAMP-elevating agents up-regulate B7.2, but not B7.1, expression in unstimulated, resting macrophages but they down-regulate B7.2 expression on LPS/IFN-γ-activated peripheral macrophages and microglia (Menendez Iglesias et al., 1997; Delgado et al., 1999). The regulation of the expression of this important T cell costimulatory signal on macrophages may represent another important mechanism of how CAs affect locally cellular immune responses in the periphery or the brain.

Thus, altogether, the Yin-Yang state of suppressive versus stimulatory effects of CAs on macrophage activities, apart from the experimental conditions, might be related to several factors, such as: presence or absence of antigen; presence in the microenvironment of pro-inflammatory mediators, such as SP, peripheral (immune) CRH, and histamine, released from the sensory neurons and mast cells; the state of activation or differentiation of macrophages all may determine the β-AR responsiveness, the expression of α-ARs, and the effect of CAs on the expression of important costimulatory molecules such as B7.2.

3. T Cytotoxic Lytic Activity. Relatively few data are available about the effect of CAs on Tc ($CD8^+$) cell cytotoxicity. Epinephrine, NE, and isoproterenol suppress the in vitro generation of anti-MOPC-315 tumor cytotoxicity by mouse splenic Tc lymphocytes (Cook-Mills et al., 1995). Increasing cAMP with either a cAMP analog or the β-ARs agonist metaproterenol significantly inhibits the in vitro development of memory Tc activity in mice using an anti-influenza cytotoxic Tc assay (Bender et al., 1993). In contrast, CAs or β-AR agonists, when added at the initiation of a 5-day sensitization phase, increased the generation of Tc-mediated cytotoxicity using the mixed lymphocyte culture method in BALB/c mice (Hatfield et al., 1986). Thus, CAs may exert enhancing effects on the initiation of Tc responses, in contrast to inhibition of effector cell function.

4. Neutrophil Functions. CAs inhibit both neutrophil phagocytosis and the release of lysosomal enzymes from neutrophils (Zurier et al., 1974). Low doses of isoproterenol also inhibit the respiratory burst of neutrophils associated with degranulation (Nielson, 1987). Furthermore the superoxide generation and formation of oxygen radicals that play an important microbicidal role are both suppressed at nanomolar concentrations of epinephrine, an effect prevented by β_2-AR blockade (Weiss et al., 1996; Barnett et al., 1997). It was revealed that β-AR stimulation decreased the maximal rate of superoxide production and increased the rate of termination of superoxide production (Gibson-Berry et al., 1993). In the presence of two powerful chemoattractants, leukotriene B4 and formyl-methionyl-leucyl-phenylalanine, β-AR stimulation also inhibits the chemotaxis of human neutrophils (Harvath et al., 1991).

E. Effect of Catecholamines and Drugs on Antibody Production (Humoral Immunity)

Binding of antigen to B cells induces an activation and subsequent proliferation and differentiation of these cells into antibody-secreting cells plasma cells. However, to proceed through these steps, the B cells require "help", and $CD4^+$ Th are the cells that provide this help through cell contact- and cytokine-mediated signals (Fig. 2). When B cells and Th cells are exposed to Th cell-dependent antigens, NE, through stimulation of β_2 receptors, exerts an enhancing effect on B cell antibody (Ab) production (Sanders, 1995; Sanders et al., 1997). One mechanism for this enhancement may involve a β_2-AR-induced increase in the frequency of B cells differentiating into Ab-secreting cells. Thus, when the

number of cells secreting anti-trinitrophenyl (TNP) IgM Ab was determined by a TNP-specific ELISPOT assay, it was found that there was about 2-fold increase in the precursor frequency of anti-TNP IgM-secreting cells in the cultures treated with terbutaline, a β_2-AR agonist (Sanders, 1998). The β_2-AR-mediated increase of intracellular cAMP may be particularly important for B cell activation and Ab production for two other reasons. First, the expression of the B7 molecule on B cells that determines the effectiveness of a T cell-B cell interaction for both T cell and B cell activation, is up-regulated by either MHC-restricted T cell interaction or by agents that elevate cAMP (Watts et al., 1993). Second, it appears that a critical *threshold* level of intracellular cAMP must be obtained before the conjugated B cell can be activated (Pollok et al., 1991). Thus, β_2-AR stimulation during the critical Th/B lymphocyte interaction may augment the cAMP in those conjugated B cells that did not reach a critical threshold level of cAMP (Sanders, 1998).

Moreover, Th cells not only activate B cells during cell-to-cell interaction, but they (Th2 cells) also provide the cytokines necessary for B cell growth. Here again CAs may play an important modulatory role through their differential effect on type 1 and type 2 cytokine production (see text above and Fig. 2). Recent studies are in support of this hypothesis. Thus, the β-AR agonists salbutamol and fenoterol potentiate IL-4 induced IgE production by human PBMC, although they inhibit IFN-γ production by these cells (Coqueret et al., 1995). Furthermore, salbutamol induces an increase of the ex vivo release of IL-4, IL-6, and IL-10 (Coqueret et al., 1994a). This might have resulted from the disinhibition of the restraining inputs of type 1 cytokines on Th2 cells and by a direct potentiation of the production of IL-6 and IL-10 by APC. Taken together, the enhancement of Ab production (and specifically of IgE by β-AR agonists) further supports the hypothesis that CAs, via β-AR stimulation selectively inhibit Th1 functions and cellular immunity and mediate a Th2 shift that potentiate humoral immunity (see also text above).

XI. Role of Growth Factors in Sympathetic Nervous System Development and Modulation of the Immune Response

Glucocorticoids, thyroid hormones, and a family of neurotrophic proteins such as nerve growth factor (NGF), neurotrophin 3 (NT3), NT4, and brain-derived neurotrophic factor (BDNF) play a major role in SNS development. Sympathoadrenal progenitors are bipotential when cultured in vitro. In the presence of NGF, they differentiate to form sympathetic neurons, and in the presence of glucocorticoids, they form chromaffin-like cells (Anderson and Axel, 1986). In fact, targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development; in glucocorticoid receptor −/− mice, not only is the capacity of chromaffin cells to synthesize epinephrine abolished, but the number of chromaffin cells are reduced substantially. This is accompanied by a normal survival of noradrenergic chromaffin cells (Cole et al., 1995). Similarly, in mice lacking a functional corticotropin-releasing hormone receptor 1, the medulla of the adrenal gland is atrophied (Timpl et al., 1998).

Thyroid hormones such as thyroxine (T4) and triiodothyronine (T3), apart from regulating energy metabolism, influence growth and development. In chromaffin cells, T3 induces the enzyme TH, which is involved in catecholamine synthesis. This action is similar but apparently independent from NGF (Timiras and Nzekwe, 1989). The production of NGF, however, is thyroid hormone-responsive, and it seems likely that some of the effects of thyroid hormones on autonomic and CNS development are mediated through induction of NGF and other growth factors (Fisher et al., 1982).

NGF was the first discovered, and so far, the best characterized neurotrophic factor for the development and differentiation of sympathetic neurons in both developing and adult animals. The essential role of NGF was first demonstrated by injecting NGF antibodies in rodents. This resulted in the death of peripheral sympathetic neurons (cf. Aloe, 1998). NT3 plays both a complimentary and overlapping role with NGF in the development and maturation of sympathetic neurons (Zhou and Rush, 1996). NGF and NT3 are neurotrophic factors that are synthesized by effector tissues and are retrogradely transported by postganglionic neurons to prevent cell death. NGF has been found in various lymphoid organs such as spleen, lymph nodes, and thymus (Aloe et al., 1997). The spleen also contains high levels of mRNA for BDNF and NT3 (Yamamoto et al., 1996). In these organs NGF apparently regulates the sympathetic neurite outgrowth toward these organs (Kannan et al., 1996). The induction of NGF production in lymphoid organs appears to be mediated partly by IL-1 (Kannan et al., 1996).

Apart from its effects on SNS development and differentiation, NGF is now known to affect cells of the immune and endocrine systems in a variety of ways (cf. Simone et al., 1999). NGF influences B- and T-lymphocyte proliferation, is an autocrine survival factor for memory B lymphocytes, stimulates immunoglobulin production, and promotes human hemopoietic colony growth factor secretion and differentiation (cf. Aloe, 1998). In addition, hypothalamic NGF concentration increases following stressful events, and it stimulates the secretion of pituitary ACTH and adrenal glucocorticoids. The circulating levels of NGF increase in inflammatory responses, in various autoimmune diseases, in parasitic infections, and in allergic diseases (Aloe et al., 1997; Aloe, 1998). Thus, this neurotrophic factor is in fact a pleiotropic cytokine that plays an important role at the interface between the nervous and the immune systems.

Recent studies indicate that NGF is synthesized by cells of immune system lineage, its level increases during inflammatory responses, and that cytokines such as IL-1 and TNF-α are potent inducers of NGF secretion (Aloe et al., 1997; Aloe, 1998). NGF-specific mRNA is present in mouse T lymphocytes of both the $CD4^+$ and $CD8^+$ phenotypes, and in splenic B cells. In $CD4^+$ cells, NGF is present in both Th1 and Th2 antigen-specific clones, but an increase of NGF-specific message is detected after antigenic challenge only in Th2 cells (Santambrogio et al., 1994). Human Th2 clones also produce and release NGF (Bonini et al., 1999). Splenic mononuclear cells from allergen-sensitized mice produced NGF in response to allergen (Braun et al., 1998). They respond to exogenously added NGF with an increase in IL-4 and IL-5 production and augmented IgE and IgG1 synthesis (Braun et al., 1998). In rat peritoneal mast cells NGF causes an increase in the mRNAs for IL-3, IL-4, IL-10, and TNF-α (Bullock and Johnson, 1996). Thus, an allergic inflammation might be accompanied by enhanced local secretion of NGF that acts as an amplifier for Th2 effector functions. This is substantiated by the observations that NGF also enhances histamine release (Bischoff and Dahinden, 1992), although NGF and IL-4 act as cofactors for IL-3-induced histamine production by basophils cells (Richard et al., 1992).

In mouse astrocytes IL-4, IL-5, and IL-10 induce an increase in NGF secretion, whereas IFN-γ, IL-2, IL-3, and IL-6 do not (Awatsuji et al., 1993; Brodie, 1996). However, IFN-γ appears to antagonize the increase in NGF secretion, induced by IL-10 (Brodie, 1996). This indicates that type 2 cytokines such as IL-4, IL-5, and IL-10 may provide neurotrophic support to injured neurons via induction of NGF synthesis. Of interest, treatment with β_2-AR agonists up-regulates NGF secretion in astrocyte cultures, and NGF appears to mediate the neuroprotective effect of the β_2-AR agonist clenbuterol in vitro and in vivo (Culmsee et al., 1999). In addition evidence was obtained (Charon et al., 1998; Cruz-Aguado et al., 1999; Culmsee et al., 1999; Matsuoka et al., 1999; Semkova et al., 1999; Silva et al., 2000) that β_2-adrenoceptor activation increases cAMP level, and it is in correlation with neuroprotection actions and NGF production (Cruz-Aguado et al., 1999; Culmsee et al., 1999; Silva et al., 2000).

XII. Physiologic Control of the Sympathetic-Immune Interface: β-Adrenergic Receptor Expression, Coupling, and Desensitization

The physiologic regulation of the sympathetic-immune interface appears to be a rather complex phenomenon, exerted at different levels. Centrally, the SNS output appears to be affected by different neurotransmitter pathways, stress, diurnal rhythms, and immune responses (see text above). Several cytokines appear to control neurotransmitter plasticity, its release, and receptor excitability at the level of the sympathetic ganglia (Jonakait, 1993). Thus, TNF-α and IFN-γ modulate nicotinic responses, Ca^{2+} currents and NE secretion and inactivation, whereas transforming growth factor (TGF)-β modulates the development of neuronal excitability by regulating the expression of voltage-gated K^+ channels in sympathetic ganglia (Soliven and Albert, 1992a,b; Soliven and Wang, 1995; Phelan et al., 1997). Furthermore, IL-1, and to a lesser extent TNF-α, induce substance P in sympathetic ganglia through the induction of leukemia inhibitory factor (Shadiack et al., 1993; Ding et al., 1995), whereas IL-6 induces about a 6-fold increase in choline acetyltransferase mRNA in cultured rat sympathetic neurons (Oh and O'Malley, 1994).

At the level of sympathetic nerve terminals, presynaptic receptors regulate the output of NE released in lymphoid organs and blood vessels (see text above and Fig. 1). Although some cytokines (such as TNF-α and IL-1) have been shown to inhibit presynaptically the release of NE in the median eminence, hippocampus, myenteric plexus, and human atria (Elenkov et al., 1992a; Hurst and Collins, 1994; Ignatowski and Spengler, 1994; Abadie et al., 1997), currently there is not enough convincing evidence that cytokines are able to modulate "presynaptically" the release of NE from the sympathetic nerve terminals in lymphoid organs. Glucocorticoids and estrogens, however, are potent inhibitors of the extraneuronal uptake of NE; thus, through this mechanism these hormones may increase local levels of CAs (Salt, 1972).

The input of the SNS on lymphoid cells can also be regulated postsynaptically at different levels: by regulation of the expression of β- and/or α-ARs and the subtype of G-protein coupled to these receptors (see text above for the differential expression of β-ARs on different subpopulations of lymphocytes and their coupling to adenylate cyclase); by regulation of both PDE and β-adrenergic receptor kinase (βARK) activity, and through the process of homologous and heterologous desensitization of G-protein-coupled receptors.

Human lymphocyte β-ARs demonstrate characteristic down-regulation after chronic treatment with β_2-AR agonists. This process appears to differ among different mononuclear cell subsets: after treatment of healthy volunteers for 7 days with terbutaline, a β_2-AR agonist, the β_2-AR number decreased by more than 50% in Tc, but the reduction was much smaller in NK and Th cells and absent in B cells. The β-AR down-regulation in these cells was related to a decreased cAMP response to isoproterenol; the cAMP generation in response to prostaglandin E1 was also reduced, suggesting heterologous type of desensitization (Maisel et al., 1989). The β-AR down-regulation appears to be relevant to in vivo conditions since Pende et al. (1991) found an inverse correlation between the β_2-AR density on mononuclear leukocytes and the basal plasma NE in healthy human volunteers.

However, both an increase and decrease of the number of β-ARs and the cAMP response to isoproterenol are reported after activation of human and murine lymphocytes with mitogens (Radojcic et al., 1991; Carlson et al., 1994; Cazaux et al., 1995). After activation of quiescent Tc clones in IL-2-containing media, the cAMP response to β_2-AR agonists, histamine, and prostaglandins increases, peaking 4 to 5 days after stimulation. Carlson et al. (1994) suggested that mitogens prevent both the sequestration of the β_2-AR and its dissociation from the G_s protein in response to isoproterenol stimulation, whereas Radojcic et al. (1991) also reported some increase in the number of β_2-ARs. In apparent contrast, a decrease in β_2-AR numbers on murine T lymphocytes and diminished response to isoproterenol at the peak of the proliferative response to a mitogen was recently reported (Cazaux et al., 1995). In vivo, immunization with bovine serum albumin (BSA) induces a reduction in the density of β-ARs 3 days after antigenic challenge, followed by a significant increase in receptor number 7 and 15 days after immunization (Morale et al., 1992). Cytokines such as IL-1α, IL-1β, and TNF-α increase the density of human β-ARs, whereas glucocorticoids also increase β-AR density and markedly potentiate the effect of these cytokines (Stern and Kunos, 1988; Nakane et al., 1990). Glucocorticoids are well known to exert a permissive effect on cAMP-elevating agents in various cell types (Malbon et al., 1988), and the gene for the human β_2-AR contains a glucocorticoid response element (Hadcock et al., 1989). Furthermore, glucocorticoids appear to sensitize cAMP formation in resting human lymphocytes by altering the AC activity (Michel et al., 1994). Other hormones, such as insulin, also up-regulate the expression of β_2-ARs and their coupling to AC in mononuclear leukocytes (Sager et al., 1990).

Recent evidence indicates that G-proteins, and the signals they regulate, such as ion channels and AC ($G\alpha_{s/i}$) and phospholipase C ($G\beta\gamma$ and $G\alpha_{11/15-16}$) are differentially regulated in lymphoid cells in a maturation- and lineage-dependent manner. As already discussed the expression of the G-proteins $G_{15\alpha}$ (murine) and $G_{16\alpha}$ (humans) has been shown to be hemopoietic lineage-restricted with particularly high expression in pre-B cell lines (Wu et al., 1995). Of interest, there is a progressive and marked down-regulation of the expression of $G_{16\alpha}$ correlating with differentiation through mature human resting B cells to "follicular" B cells (Grant et al., 1997). Murine thymocytes, splenic T cells, and human tonsillar T cells show little or no protein expression of any of the $G\alpha$ isoform tested, except $G\alpha_s$, whereas $G\alpha_{i1}$ seem to be expressed in the late stages of human B cell development (Grant et al., 1997). Although it is a matter of speculation, since $G\alpha_s$ stimulate AC, whereas $G\alpha_i$ inhibit its activity, this may explain the differences in cAMP responses between T and B cells, and particularly the poor or absent cAMP response in B cells (see text above).

On the other hand, since cAMP is considered antiproliferative and although there does not appear to be an absolute correlation between proliferation and decreased $G\alpha_s$ expression, the process of cell activation and proliferation appears to involve down-regulation of $G\alpha_s$ and increased expression of $G\alpha_I$ in activated or proliferating B and T cells (Grant et al., 1997). These findings may suggest that altered G-protein expression may provide a mechanism for "escaping" the anti-proliferative signal, cAMP; i.e., presumably the CAs-β-ARs-cAMP pathway in activated or transformed lymphoid cells.

Agonist-induced increases in cAMP-PDE activity represent a potentially important mechanism of functional desensitization. Prolonged β-AR stimulation has been reported to up-regulate cAMP-PDE activity in human monocytes, accompanied by a mirror-image decrease in cAMP responsiveness (Chan et al., 1982). Although resting monocytes expressed both mRNA and protein for PDE4A, PDE4B, and PDE4D, prolonged β-AR stimulation up-regulated the message for PDE4A and PDE4B, whereas mRNA for PDE4D was not detected in treated cells (Manning et al., 1996).

Cellular responses to many hormones and neurotransmitters wane rapidly despite continuous exposure of cells to these stimuli. This phenomenon is termed desensitization. In the case of β-AR desensitization this process does not appear to require internalization of the receptors, but rather an alteration in the functioning of β-ARs themselves that uncouples the receptors from the stimulatory G-protein G_s. Two patterns of rapid desensitization have been characterized for G-protein-coupled receptors: homologous desensitization, which mainly involves G-protein-coupled receptor kinases (GRK) and arrestins, and heterologous desensitization, which mainly involves PKA and PKC (Chuang et al., 1996). βARK is a serine-threonine kinase involved in the process of homologous desensitization of G-protein-coupled receptors. βARK is a member of a multigene family, consisting of six known subtypes, also named GRKs (De Blasi et al., 1995). Among the six known GRKs, four (GRK-2, GRK-3, GRK-5, and GRK-6) are highly expressed in peripheral blood leukocytes. Agonist occupancy triggers translocation of βARK from cytosol to plasma membranes, where it phosphorylates agonist-occupied receptors. A substantial increase of βARK is observed after stimulation of lymphocytes with mitogens, a process that appears to be PKC-mediated. A significant increase in βARK1 and βARK2, but not GRK-5 and GRK-6, was observed 48 h after mitogen stimulation (De Blasi et al., 1995). Of interest, a recent study by Daaka et al. (1997) performed in HEK293 cells, demonstrates that a mechanism previously shown to mediate uncoupling of the β_2-AR from G_s and thus heterologous desensitization (PKA-mediated receptor phosphorylation), also serves to "switch" coupling of this receptor from G_s to G_i, and, thus, initiate a new set of signaling events.

In summary, the expression of β-ARs on lymphoid cells and their coupling to different G-proteins and intracellular effectors is a dynamic process that depends of the state of activation and differentiation of the cell and appear to be subject to regulation by several endogenous ligands, such as CAs, different hormones, and cytokines. Since the level of these endogenous ligands varies during an immune response, the regulation of β- or α-ARs might have physiological and pathophysiological importance and it may participate in regulatory mechanisms.

XIII. Clinical Implications

A. Infections

A major factor governing the outcome of infectious diseases is the selection of Th1 versus Th2 predominant adaptive responses during and after the initial invasion of the host (Abbas et al., 1996; Fearon and Locksley, 1996; Mosmann and Sad, 1996). Thus, hyperactive SNS or stress-related increases of CA levels through induction of a Th2 shift may have a profound effect on the susceptibility of the organism to and/or may influence the course of an infection, the defense against which is primarily through Th1-driven cellular immunity mechanisms (Table 5).

Cellular immunity, and particularly IL-12 and IL-12-dependent IFN-γ secretion in humans, seems essential in the control of mycobacterial infections (Altare et al., 1998). In the 1950s, Thomas Holmes (cf. Lerner, 1996) reported that individuals who had experienced stressful life events were more likely to develop tuberculosis and less likely to recover from it. Although it is still a matter of some speculation, stress hormone-induced (CAs and glucocorticoids) inhibition of IL-12 and IFN-γ production and the consequent suppression of cellular immunity may amply explain the pathophysiologic mechanisms of these observations (Elenkov et al., 1996; Elenkov and Chrousos 1999).

Helicobacter pylori infection is the most common cause of chronic gastritis, which in some cases progresses to peptic ulcer disease. The role of stress in promoting peptic ulcers has been recognized for many years (see Levenstein, 1998; Levenstein et al., 1999) Thus, increased systemic CAs and glucocorticoid levels, in concert with an increased local concentration of histamine, induced by inflammatory or stress-related mediators, may skew the local responses toward Th2 and, thus, allow the onset or progression of a *H. pylori* infection (Elenkov et al., 1998).

HIV+ patients have IL-12 deficiency versus elevated levels of IL-10, whereas disease progression has been correlated with a Th2 shift (cf. Haraguchi et al., 1995a). The innervation (primarily sympathetic/noradrenergic) of lymphoid tissue may be particularly relevant to HIV infection, since lymphoid organs represent the primary site of HIV pathogenesis. In fact, NE, the major sympathetic neurotransmitter released locally in lymphoid organs (see text above) was recently reported to directly accelerate HIV-1 replication by up to 11-fold in acutely infected human PBMCs (Cole et al., 1998). The effect of NE on viral replication is transduced via the β-AR-AC-cAMP-PKA signaling cascade (Cole et al., 1998). In another recent study Haraguchi et al. (1995a,b,c) found that the induction of intracellular cAMP by a synthetic, immunosuppressive, retroviral envelope peptide caused a shift in the cytokine balance and led to suppression of cell-mediated immunity by inhibiting IL-12 and stimulating IL-10 production. Thus, on one hand CAs may suppress cellular immunity and directly accelerate HIV replication, whereas, in contrast, retroviruses may suppress cell-mediated immunity using the same pathways by which CAs alter the Th1/Th2 balance.

In a recent study, an association was demonstrated between stress and the susceptibility to the common cold among 394 persons who had been intentionally exposed

TABLE 5

Putative pathophysiologic roles of CA-induced alterations of Th1/Th2 balance in certain infections, infectious complications after major injury, autoimmune/inflammatory, allergic or neoplastic diseases (modified from Elenkov and Chrousos, 1999)

Condition	Host Response	Pathogenic Response	Role of CAs and Stress
Infections Mycobacterium tuberculosis Helicobacterium pylori HIV Common cold viruses	Th1 protects	Suppressed cellular immunity, deficit of IL-12 and IFN-γ, Th2 shift with progression of infection	Stress-induced increase of CAs levels and subsequent Th2 shift may contribute to increased susceptibility to or progression of these infections
Major injury	Th2 protects?	Suppressed cellular immunity and IL-12, and IFN-γ production, overproduction of IL-10, Th2 shift	Increased levels of CAs may contribute to suppression of cellular immunity resulting in infectious complications
Autoimmunity Rheumatoid arthritis Multiple sclerosis Autoimmune thyroid disease Type 1 diabetes mellitus	Excessive Th1 response	Th1 shift, overproduction of IL-12, TNF-α, IFN-γ; deficit of IL-10	A hypoactive SNS may facilitate/sustain the Th1 shift and flares of these autoimmune diseases[a]
Tumors	Th1 protects	Suppressed cellular immunity, deficit of IL-12, TNF-α, overproduction of IL-10 and TGF-β	Hyperactive SNS and CA-induced Th2 shift may contribute to increased susceptibility to or progression of certain tumors

[a] The role of SNS in autoimmunity is more complex; see text for details.

to five different upper respiratory viruses. Psychological stress was found to be associated in a dose-dependent manner with an increased risk of acute infectious respiratory illness, and this risk was attributed to increased rates of infection rather than to an increased frequency of symptoms after infection (Cohen et al., 1991). Thus, stress hormones (CAs and glucocorticoids) through their selective inhibition of cellular immunity (Elenkov et al., 1996) may play substantial roles in the increased risk of an individual to acute respiratory infections caused by common cold viruses.

B. Major Injury

Major injury (serious traumatic injury and major burns) or major surgical procedures often lead to severe immunosuppression that contributes to infectious complications and, in some cases to sepsis, the most common cause of late death after trauma. The neuroendocrine response is an essential component of the adaptive process to trauma, brain injury, and major surgery. Generally, after brain or extracerebral injury there is a biphasic pattern of response, with a sympathoadrenal storm associated with variable and altered stimulation of the HPA axis during the ebb phase; the first phase is followed by a decrease in both responses (Chiolero and Berger, 1994). It is important that the intensity of these changes (particularly with CAs and cortisol plasma levels) correlates with the severity of both cerebral and extracerebral injury and an unfavorable prognosis (Jarek et al., 1993; Chiolero and Berger, 1994; Rothwell and Lawler, 1995; Rothwell et al., 1996). In patients with traumatic major injury and in animal models of burn injury, the suppressed cellular immunity is associated with diminished production of IFN-γ and IL-12 and increased production of IL-10, i.e., a Th2 shift (O'Sullivan et al., 1995). This is further substantiated by the observation that TNF-α production is reduced in LPS-stimulated whole blood after trauma (Fabian et al., 1995), whereas the production of type 1 cytokines, such as IFN-γ, TNF-α, and IL-2, is down-regulated on postoperative day 1 after conventional but not laparoscopic surgery (Brune et al., 1999). A recent study by Woiciechowsky et al. (1998) indicated that systemic release of IL-10 triggered by SNS activation might be an important mechanism of immunosuppression after injury. Thus, high levels of systemic IL-10 documented in patients experiencing a "sympathetic storm" due to acute accidental or iatrogenic brain trauma were associated with high incidence of infection. Furthermore, this study demonstrates that the β-AR blockade by propranolol dose dependently inhibited CA-induced release of IL-10 and prevented the increase of circulating IL-10 in the rat model (Woiciechowsky et al., 1998).

Therefore, all the above-mentioned data suggest that CA secretion triggered by major injury, via an induction of a Th2 shift, may contribute to the severe immunosuppression observed in these conditions. As recently stated by Plata-Salaman (1998), these observations may have two important implications: 1) they provide direct evidence in humans of a neuroendocrine pathway, the sympathoadrenal system coupled with a systemic immunosuppressive response that triggers high incidence of infections and complications; 2) they emphasize the importance of neurotransmitter/hormone-associated modulation of immunity.

C. Adrenergic Agents, Sepsis, and Nitric Oxide Generation

As mentioned above, the suppression of host defense mechanisms associated with major surgery or trauma was proposed to determine susceptibility to infectious complications and to the development of sepsis. Apart from suppression of type 1 cytokines and potentiation of type 2 cytokine production, major surgery and trauma was also associated with impaired lymphocyte proliferation, delayed-type hypersensitivity skin test response, cell surface MHC class II antigen expression, and suppressed neutrophil functions, including chemotaxis, phagocytosis and oxygen radical production. During established sepsis, however, hyporeactivity of the immune system may be followed by a state of hyperactivity that is characterized by the excessive production of multiple inflammatory cytokines and is associated with high mortality. The molecular mechanisms responsible for this functional conversion of the immune system have not been identified as yet (cf. Hensler et al., 1998).

In the case of Gram-negative bacterial sepsis, the pro-inflammatory cytokines TNF-α and IL-1, produced in response to endotoxin, appear to be critical components in the dysregulated host response during sepsis. It is believed that these cytokines trigger a cascade of events, including synthesis of prostaglandins, leukotrienes, reactive oxygen metabolites, and platelet-activating factor (PAF) that results in septic shock and multiple organ dysfunction syndrome. An important point is that TNF-α appears to be a key mediator of enhanced NO production by the macrophage-type inducible nitric oxide synthase that contributes to the development of hypotension, peripheral vasodilatation, and vascular hyporeactivity to vasoconstrictor agents in endotoxin shock. However, thus far, the results of anti-TNF-α strategies, the administration of IL-1 receptor antagonist, as well as inhibitors of PAF and NO have been largely disappointing and failed to demonstrate a survival benefit (Pastores et al., 1996; Eigler et al., 1997). This may be related, in part, to the incomplete understanding of the complex timing of mediator release and balance during sepsis.

The differential effects of α_2-AR antagonists and β_2-AR agonists on type 1 and type 2 cytokine production, such as inhibition of TNF-α, IL-12 and augmentation of IL-10 production (see *Section X.B.*), clearly offers a potential for pharmacologic manipulation of cytokine production during septic shock. The first study to examine

the effect of epinephrine pretreatment on cytokine production in healthy human volunteers challenged with endotoxin in vivo confirmed the inhibition of TNF-α appearance and increase in IL-10 release (van der Poll et al., 1996). Furthermore, isoproterenol, not a subtype selective β-AR agonist, appears to suppress NO production by macrophages and prevents the LPS-induced suppression of vascular contractility to NE in the thoracic aorta ex vivo (Szabó et al. 1997; Hasko et al. 1998a).

Pharmacological cardiovascular support of human septic shock is currently not well standardized (Pastores et al., 1996). Such support includes the administration of α-adrenergic agonists to maintain perfusion pressure, β-adrenergic agonists (including dobutamine, which acts mostly as a β_1-AR agonist) to improve cardiac output and oxygen delivery; and dopamine-receptor agonists to augment renal and mesenteric perfusion (for more details see Pastores et al., 1996). Despite early claims of improved outcome, more recent studies add a word of caution regarding the use of dobutamine and suggest worsening survival and increased end-organ injury (Hayes et al., 1994). Moreover, in humans, β_2- but not β_1-ARs appear to control monocyte/macrophage cytokine profiles. Therefore, currently, a clear recommendation for a specific catecholamine regimen in septic shock is impossible. Systemic examination will be necessary to determine the combination and the right choice of adrenergic agents that would satisfy an optimal balance between cardiovascular support and immunomodulation during septic shock.

Further complexity is added by the recent observations of Hensler et al. (1998) showing that low preoperative IL-12 secretion by monocytes precedes the onset of sepsis. This is consistent with the concept discussed above that suppression of both innate and T cell-dependent mechanisms predisposes patients with major surgery or trauma for the development of septic complications. Furthermore, recently obtained in vitro evidence indicates that CAs can dramatically increase the growth of Gram-negative bacteria such as *Escherichia coli* and *Yersinia enterocolitica* (cf. Lyte, 1992). Thus, an early intervention and suppression of IL-12 production and possibly an increase in bacterial growth by application of adrenergic agents might even have a harmful effect.

Recent studies applying anti-TNF-α strategies demonstrated that patients with high systemic levels of IL-6 might benefit most from anti-cytokine therapy (cf. Eigler et al., 1997). Therefore, patient stratification based on the individual inflammatory response condition should greatly improve the benefits of immune therapy. Thus, it was proposed that immune stimulatory protocols should prove beneficial for patients showing hyporeactive immune response conditions (a Th2 shift?), whereas patients with a hyperactive immune system (a Th1 shift?) may selectively benefit from anti-inflammatory therapy (Hensler et al., 1998). In conclusion, patient stratification, the right choice of timing, and type of intervention, including adrenergic agents, might be an important factor in determining the success of therapeutic strategies in sepsis and its complications (see *Section XIII.B.* and the beginning of this section).

D. Autoimmunity

Several autoimmune diseases are characterized by common alterations of Th1 versus Th2 and IL-12/TNF-α versus IL-10 balance (Table 5). In rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes mellitus, autoimmune thyroid disease (ATD) and Crohn's disease the balance is skewed toward Th1 and an excess of IL-12 and TNF-α production, whereas Th2 activity and the production of IL-10 are deficient (Wilder, 1995; Mosmann and Sad, 1996; Elenkov et al., 1997). This appears to be a critical factor that determines the proliferation and differentiation of Th1-related autoreactive cellular immune responses in these disorders (Segal et al., 1998). On the other hand, systemic lupus erythematosus (SLE) is associated with a Th2 shift and an excessive production of IL-10, whereas IL-12 and TNF-α production appear to be deficient (Maini et al., 1994; Horwitz et al., 1998).

The autonomic/sympathetic nervous system and HPA axis, both involved in stress responses, influence autoimmunity in a complex way (Arnason et al., 1988; Chrousos, 1995; Wilder, 1995; Rogers and Fozdar, 1996). In consideration of Th2-driving effects of CAs systemically, one could postulate that a hypoactive SNS may facilitate/sustain the Th1 shift in MS or RA, and vice versa, SNS hyperactivity may intensify the Th2 shift and induce/facilitate flares of SLE. Animal studies and certain clinical observations support this hypothesis. Thus, Fischer (F344) rats, which have a hyperactive stress system, are extremely resistant to experimental induction of Th1-mediated autoimmune states, including arthritis, uveitis, and experimental allergic encephalomyelitis (EAE) (Wilder, 1995). Similarly, women in the third trimester of pregnancy, who have increased levels of cortisol and probably CAs (Cohen et al., 1988; Magiakou et al., 1996), experience remission of Th1 type-mediated autoimmune diseases, such as RA, MS, type 1 diabetes mellitus, and ATD, possibly via suppression of pro-inflammatory and potentiation of anti-inflammatory cytokine production. Through a reciprocal mechanism, Th2 type-mediated autoimmune disorders mainly driven by IL-10, such as SLE, may flare in high cortisol and CAs output states, i.e., during stress or pregnancy (Wilder, 1995; Elenkov et al., 1997). There are different opinions (Lin et al., 1993; Sacks et al., 1998, 1999) suggesting that there is dysregulation between the maternal nonspecific and specific immune responses.

Conversely, Lewis (LEW) rats, which exhibit a hypoactive stress system are extremely prone to develop experimentally induced Th1-mediated states, such as arthritis, uveitis, or EAE (Wilder, 1995). Similarly, clinical

situations associated with blunted stress system activity are associated with heightened susceptibility to or activity of Th1 type-mediated autoimune diseases such as RA, MS, and ATD. This might include the postpartum period and the period that follows cessation of chronic stress or a rebound effect upon relief from stressors (Chrousos, 1995; Wilder, 1995; Elenkov et al., 1996).

Several lines of evidence suggest that the sympathetic-immune interface is defective in MS and its experimental model, EAE. Thus, sympathetic skin responses are decreased and lymphocyte β-ARs are increased in progressive MS (Karaszewski et al., 1990). The density of β-ARs on $CD8^+$ T cells are increased between 2- and 3-fold, compared with age-matched controls; no changes of the density of these receptors on monocytes, B cells, and $CD4^+$ cells were observed (Arnason et al., 1988; Karaszewski et al., 1993). Similarly, in the preclinical stage of EAE the NE content in spleen is reduced, accompanied by an increase of splenocyte β-ARs density (Mackenzie et al., 1989). A defective or hypoactive SNS is most likely to be a "causative" factor for the up-regulation of β-ARs observed in MS (Arnason et al., 1988); however, the "up-regulating" effects of cortisol or IL-1 on β-ARs receptor expression cannot be ruled out (Zoukos et al., 1992).

The "protective" role of the SNS is further substantiated by the observations that chemical sympathectomy augments the severity of EAE (Chelmicka-Schorr et al., 1988), whereas a uniformly increased splenic NE content was observed at peak disease (Leonard et al., 1991). Neurochemically it means that the release of NE was reduced, giving further support that SNS is protective in EAE. Moreover, chemical sympathectomy with 6-OHDA produced a significant depletion of splenic NE alone, which resulted in increased disease severity, despite the fact that circulating glucocorticoids were elevated. Furthermore, isoproterenol and terbutaline, β-AR and β_2-AR agonists, respectively, were reported to suppress chronic/relapsing EAE in LEW rats (Chelmicka-Schorr et al., 1989; Wiegmann et al., 1995). The latter observation might have resulted from the previously discussed effects of CAs and β-AR agonists on the production of type 1 cytokines. This is further substantiated by recent evidence that the drug rolipram, by selective inhibition of phosphodiesterase type IV and subsequently the production of type 1/pro-inflammatory cytokines, such as TNF-α, IFN-γ, and IL-12, prevents and ameliorates the course of EAE (see text below).

The role of SNS in RA is less clear and more controversial. In a recent study, Baerwald et al. (1997) demonstrated that in RA patients the number of β-ARs on $CD8^+$ lymphocytes, but not on $CD4^+$ lymphocytes, was significantly decreased compared with cells from healthy donors. An even more pronounced decrease of β-ARs on synovial fluid lymphocytes compared with peripheral lymphocytes was also observed. Furthermore, these changes were accompanied by a diminished effect of CAs on OKT3-induced PBMC activation, suggesting a functional significance of β_2-AR alterations. Thus, it was suggested that impaired control of the immune response by the ANS may contribute to the pathogenesis of RA (Baerwald et al., 1997). In contrast, Lombardi et al. (1999) failed to observe differences of β-AR number on PBMC between RA patients and healthy donors. Interestingly, they found a decrease in GRK activity in RA subjects that was mirrored by a decrease in GRK-2 and GRK-6 protein expression. The decrease in GRK-2 activity appears to be mediated by cytokines such as IL-6 and IFN-γ. Thus, local pro-inflammatory cytokines or altered activity of the SNS may mediate changes in coupling of β-ARs to G-proteins observed in RA patients.

In the arthritis-prone LEW rats, sympathectomy with 6-OHDA enhanced the severity of adjuvant-induced arthritis (Felten et al., 1992). In this animal model of arthritis, selective sympathetic denervation of the reactive secondary lymphoid organs (the popliteal and inguinal lymph nodes) was achieved with local injection into the fat pads surrounding these lymph nodes (Felten et al., 1992). This denervation resulted in earlier onset and enhanced severity of inflammation and bone erosions compared with nondenervated rats. In contrast, Levine et al. (1988) provided evidence in adjuvant-induced arthritis in Sprague-Dawley rats that chronic administration of the β-AR blocker propranolol induced a delayed onset and attenuation of the severity of joint injury.

These discrepancies might have resulted from different experimental conditions, rat strain differences in sensitivity and susceptibility to experimentally induced arthritis, a nonspecific effect of rather high doses of propranolol used in the study of Levine et al. (1988), or more likely, they may reflect the complex regulation of macrophage functions by the SNS (see text above). As already mentioned, the SNS alone, or in conjunction with secretory mediators from sensory neurons might up-regulate, at some point, local macrophage functions and/or type 1 cytokine production that may trigger an exacerbation of disease activity. Thus, the systemic effect of the SNS might be different from certain local responses, and particularly the effect of sympathetic innervation in the joints. The local effect of the SNS in the joints might even be different from the local effect of CAs, centrally, in microglia or astrocytes (see above). In addition, the role of the SNS at the time of the induction of experimental arthritis, including its effect on type 1 cytokine production might be distinct from its role much later in the effector phase. Thus, during an established arthritis local inflammatory mediators may directly affect sympathetic nerve terminals releasing pro-inflammatory mediators.

In fact, recent evidence indicates that continuous perfusion of bradykinin induces significant plasma extravasation in the knee joint of the rat (Green et al., 1994). Employing this experimental model of inflammation, it has been suggested that the potent inflammatory

mediator bradykinin acts on postganglionic sympathetic nerve terminals to cause the release of mediators (specifically PGE2), which then promote inflammation (Green et al., 1998). Interestingly, the action of bradykinin to produce plasma extravasation via a sympathetic mechanism was found not to require electrical activity in sympathetic neurons and was not dependent on vesicular release of the neurotransmitter NE (Miao et al., 1996). Thus, peripheral sympathetic terminals may have two different functions: the classical transmission of impulse activity with concomitant release of NE and mediation of inflammatory processes, independent of activity and neurotransmitter vesicular release (Green et al., 1998). Another important local factor might be the presence of mast cells in joints (Malone et al., 1987). Thus, locally, in the RA synovium stress- or inflammation-induced release of certain mediators released from both sympathetic and sensory nerve terminals, such as SP and CRH (Malone et al., 1987) might exert potent pro-inflammatory effects via release of histamine from mast cells (Theoharides et al., 1995, 1998; Elenkov et al., 1999). Certainly, the above-mentioned discrepancies about the role of SNS in RA demand further studies.

However, a recent study suggests that the protective role of the SNS in RA might prevail over the "permissive" one. Thus, Malfait et al. (1999) demonstrated that the β_2-AR agonist salbutamol is a potent suppressor of established collagen-induced arthritis in mice. This drug had a profound protective effect as assessed by clinical score, paw thickness, and joint histology. Additionally, in in vitro experiments salbutamol reduced IL-12 and TNF-α release by peritoneal macrophages and blocked mast cell degranulation in joint tissues.

E. Fibromyalgia and Chronic Fatigue Syndrome

Patients with unexplained chronic pain and/or fatigue have been described for centuries in the medical literature, although the terms used to describe these symptom complexes have changed frequently. The currently preferred terms for these syndromes are fibromyalgia and chronic fatigue syndrome (CFS) (for details see Clauw and Chrousos, 1997).

Fibromyalgia is the second most common rheumatologic disorder, behind osteoarthritis. To fulfill the criteria for fibromyalgia, an individual must have both chronic widespread pain and the presence of "tender points" on examination. The current definition of CFS requires that the affected individual display severe chronic fatigue without a defined cause, as well as the presence of four of the eight following symptoms: myalgia, arthralgia, sore throat, tender nodes, cognitive difficulty, headache, postexertional malaise, or sleep disturbance (cf. Clauw and Chrousos, 1997). There has been little study of underlying pathophysiologic mechanisms of fibromyalgia and CFS. Clauw and Chrousos (1997) recently suggested that a blunting of human stress response predisposes and/or mediates these syndromes. This may be manifested as: blunting of one or more hypothalamic-pituitary axes, globally increased peripheral and/or visceral nociception, or instability of the autonomic nervous system. In fact, several lines of evidence indicate that a dysregulation of the autonomic nervous system might play a role in fibromyalgia. Thus, muscle sympathetic activity appears to be reduced in fibromyalgia (Elam et al., 1992). Qiao et al. (1991) demonstrated decreased microcirculatory vasoconstrictor responses to both cold and auditory stimulation and a high baseline skin conductance. More recently, a blunted sympathetic response to stressors was reported when heart rate variability or tilt table testing has been used to analyze autonomic responses (Clauw et al., 1996a,b). Perhaps the most consistent finding regarding autonomic function is that fibromyalgia patients have an impaired sympathetic ability to respond to stressors such as exercise, muscle contraction, and noise (Qiao et al., 1991; Elam et al., 1992; van Denderen et al., 1992). The autonomic nervous system has not been as extensively studied in CFS, although these patients have been found to experience a high prevalance of neurally mediated hypotension on tilt table testing, which is related to autonomic dysfunction (Rowe et al., 1995), since α_2-AR antagonists increase sympathetic outflow (see *Section XIV.*) and inhibit TNF-α production (Haskó et al., 1995a; Elenkov et al., 1996). Taking these interactions into account, α_2-AR antagonists are recommended for the treatment of fibromyalgia and chronic fatigue syndrome.

F. Tumor Growth

The amount of IL-12 available at the tumor site appears to be critical for tumor regression (Colombo et al., 1996). Thus, low levels of IL-12 have been associated with tumor growth, as opposed to tumor regression observed with administration of IL-12 delivered in situ or systemically. On the other hand, local overproduction of IL-10 and TGF-β, by inhibiting the production of IL-12 and TNF-α and the cytotoxicity of Tc, NK cells, and macrophages, seems to play an inappropriate immunosuppressive role, allowing increased malignant tumor growth (Chouaib et al., 1997). These and others studies suggest that local and/or systemic Th1 functions and cellular immunity are down-regulated during tumor growth.

Few recent studies suggest that CA-mediated effects might be involved in an increased susceptibility to tumors, tumor growth, and metastases. In animals, β-AR stimulation suppresses NK cell activity and compromises resistance to tumor metastases (Shakhar and Ben-Eliyahu, 1998), whereas stress has been reported to decrease the potential of spleen cells to turn into antitumor Tc against syngeneic B16 melanoma, and it significantly suppresses the ability of tumor-specific $CD4^+$ cells to produce IFN-γ and IL-2 (Li et al., 1997). Mice subjected to unilateral superior cervical ganglionectomy showed slowed growth of two breast cancer lines after

implantation in the sympathetically denervated skin (Romeo et al., 1991). In humans, the augmentation of the rate of tumor progression and cancer-related death has been associated with stress (cf. Li et al., 1997). In nonmedicated advanced cancer, patients showing long symptomless periods had all normal values, whereas those who remained free of symptoms for only a short time had raised NE, epinephrine, and cortisol levels (Lechin et al., 1990). These data suggest that CA-mediated suppression of cellular immunity may play a role in increased growth of certain tumors.

XIV. Pharmacological Manipulation of the Sympathetic-Immune Interface

In the CNS, the adrenergic inhibition of sympathetic discharges is assigned to α_2-ARs. The release of NE from varicosities of sympathetic nerve terminals in response to axonal activity is subjected to negative feedback modulation via α_2-ARs (Starke, 1981): NE released from the varicosity reduces its own release. It has been shown that the presynaptic α_2-ARs, responsible for negative feedback modulation of NE release (Elenkov and Vizi, 1991; Hasko et al., 1995b), are sensitive to prazosin, an $\alpha_{2B/C}$ antagonist (cf. Docherty, 1998), and sympathetic varicose terminals do not make synaptic contact with the immune cells. A very similar interaction exists between noradrenergic varicosities and other neurons (cf. Vizi and Kiss, 1998; Vizi, 2000).

Thus, application of selective α_2-AR antagonists brings about a type of disinhibition that results in increased release of NE and increased sympathetic output (cf. Vizi, 1979, 2000; Vizi and Labos, 1991). We have shown that mice treated with the highly selective α_2-AR antagonist CH-38083 (Vizi et al., 1986) showed a blunted LPS-induced TNF-α response (Hasko et al., 1995a; Elenkov et al., 1996). This effect was blocked by propranolol, indicating that the excessive stimulation of β-ARs is responsible for the action of the α_2-AR antagonist. In addition, in in vivo condition, it was also shown that α_2-AR activation by clonidine (Szelényi et al., 2000a,b) increased TNF-α production that had been reduced by isoproterenol in mice pretreated with reserpine. Under this condition, the sympathetic innervation is impaired by reserpine, and the effect of clonidine can be as direct effect on cells producing TNF-α. These findings together with those obtained with α_2-AR antagonists (Haskó et al., 1995a; Elenkov et al., 1996) suggest that the plasma levels of TNF-α, i.e., the in vivo production of this cytokine mainly directed by NE(E) via β_2-ARs overcoming α_2-ARs. The central stimulant and sympathomimetic amphetamine evokes the release of NE by displacing cytoplasmic NE, which is released by a carrier-mediated process from the noradrenergic nerve terminal. It has been shown that in vivo administration of this drug inhibits the proliferative response of mouse lymph node cells and IL-2 production from spleen cells (Heilig et al., 1993).

Morphine administration activates the sympathoadrenal system and increases plasma CA concentration via stimulation of opioid μ-receptors at discrete hypothalamic and brainstem sites (cf. Bencsics et al., 1997a). Thus, morphine, apart from this direct effect, may exert immunomodulatory properties via stimulation of SNS. In fact, recent studies in mice indicate that the suppressive effect of morphine, in vivo, on the proliferative response of splenic cells to mitogens or LPS-induced TNF-α production was prevented by chlorisondamine, a ganglionic blocker or β-AR antagonists, suggesting that these effects require intact sympathetic outflow (Fecho et al., 1993, 1996; Bencsics et al., 1997a). In addition, it appears that morphine potentiates the β-AR responsiveness of human mononuclear cells through stimulation of μ-receptors (Pende et al., 1995).

Peripherally, the pharmacological modulation of the sympathetic-immune interface can be achieved at different levels. As already discussed, the release of NE in lymphoid organs can be modulated via several presynaptic receptors. For example, the application of the highly selective α_2-AR antagonist CH-38083, by blocking the presynaptic negative feedback exerted by NE, increases the release of endogenous NE in lymphoid organs (Elenkov and Vizi, 1991; Vizi et al., 1995). This presynaptic effect may contribute, at least in part, to the above-mentioned inhibitory effect of this drug on TNF-α production, in vivo. Prazosin, an α_1 (but also an $\alpha_{2B/C}$-AR antagonist) had a similar effect on TNF-α production in mice (Elenkov et al., 1996). Neomycin, gentamycin, and streptomycin, aminoglycoside antibiotics induce high affinity agonist binding of G_s-protein-coupled β-AR receptors (Herrmann et al., 1989). Thus, these antibiotics may amplify the effect of CAs transmitted via G-protein-coupled β-ARs.

Moreover, isoproterenol, a β-AR agonist, inhibits LPS-induced TNF-α production while potentiating IL-6 and IL-10 production in mice (Elenkov et al., 1995; Hasko et al., 1995a, 1998a). Treatment with the β_2-AR agonist salbutamol inhibits IL-12 production in humans while potentiating the ex vivo release of Th2-type cytokines in mice (Panina-Bordignon et al., 1997). These effects of β-AR agonists might be related to the already mentioned beneficial effect of isoproterenol in EAE (see text above). The β-AR antagonist propranolol removes the inhibitory effect of endogenously released NE on cytokine-producing cells, and is able to significantly increase the TNF-α and IL-12 production induced by LPS in mice in a dose-dependent manner (Elenkov et al., 1995; Hasko et al., 1998a).

Rolipram, an antidepressant extensively studied in humans, also increases the intracellular availability of cAMP in lymphoid cells by selective inhibition of phosphodiesterase type IV. Several recent studies indicate that this drug inhibits, both in vitro and in vivo, the

production of type 1/pro-inflammatory cytokines, such as TNF-α, IFN-γ, and IL-12 (Ross et al., 1997; Hasko et al., 1998b; Liang et al., 1998). These effects, however, are independent from the simultaneous increase of IL-10 production (Ross et al., 1997; Hasko et al., 1998b). Moreover, the suppressive effects of this drug on type 1 cytokines, in parallel with the increase of IL-10 have been recently linked to rolipram-induced prevention and amelioration of the course of experimental collagen-induced arthritis and EAE in rodents and nonhuman primates, and diabetes in NOD mice (Genain et al., 1995; Ross et al., 1997; Liang et al., 1998). Recent evidence indicates that all these experimental models of autoimmune diseases are driven by overproduction of type 1 cytokines, particularly IL-12 and TNF-α (Segal et al., 1998).

XV. Conclusions

The presence of sympathetic/noradrenergic nerve fibers in lymphoid organs, the release of NE from the sympathetic nerve terminals in these organs, and the expression of adrenoreceptors on lymphoid cells, which are able to respond functionally to stimulation, suggests that NE may meet the criteria for neurotransmitter/neuromodulator in lymphoid organs. The varicose axon terminals of the sympathetic nerve do not make synaptic contact with immune cells. Similar to many organs in the periphery, the release of NE is subject to presynaptic modulation via $\alpha_{2A/C}$-ARs. NE released from sympathic axon terminals diffuses far away from the release site; therefore NE transmits its signals nonsynaptically. Thus, the SNS may provide major integrative and regulatory pathway between the CNS and the immune system.

Sympathetic-immune interactions are undoubtedly complex. A few recent studies suggest that endogenous CAs modulate the function of primary lymphoid organs, such as the bone marrow and the thymus. However, the role of sympathetic innervation and endogenous CAs in regulation of hematopoiesis and thymocyte development remains poorly understood. In addition, there is almost complete lack of knowledge about how CAs might affect mucosal immunity.

Evidence accumulated in the last decades indicates that, peripherally, both NE released from the nonsynaptic sympathetic nerve terminals in lymphoid organs and blood vessels and epinephrine released from the adrenal medulla are involved in *fine tuning* of immune responses. Very similarly, steroid synthesis and secretion in the adrenal cortex is also under direct local tuning by NE and/or DA released from nonsynaptic noradrenergic varicosities in the zona glomerulosa. Morphological and neurochemical evidence indicates that a substantial proportion of the noradrenergic nerve endings lie in close proximity to zona glomerulosa cells without making synaptic contact, thus providing evidence for a direct local modulatory role of catecholamines in steroid secretion (Vizi et al., 1992, 1993; Bornstein and Vaudry, 1998; Szalay et al., 1998; Vizi, 1998). These noradrenergic neurons, like other noradrenergic neurons in the central nervous system, are able to take up DA, convert it partly into NE, and to release both NE and DA together with the cotransmitter ATP when neuronal activity drives them to do so (Vizi et al., 1993).

The effects of CAs are quick, within minutes. This modulation might be ideally designed for quick adjustment of immune responsiveness. Another important role of CAs in the periphery might be a *tonic inhibition* of certain immune functions, and particularly, the production of type 1/pro-inflammatory cytokines. Importantly, CAs appear to exert systemically differential, opposite effects on cellular and humoral immunity. By inhibiting type 1 and potentiating type 2 cytokine production and by acting directly on effector cells, CAs suppress cellular and boost humoral immunity. The Th2-driving effects of CAs may have, however, under certain conditions, both beneficial and detrimental consequences.

Although interest in the Th2 response was initially directed at its protective role in helminthic infections and its pathogenic role in allergy, this response may have important regulatory functions in countering the tissue-damaging effects of macrophages and Th1 cells (Fearon and Locksley, 1996). Thus, the above-mentioned Th2-driving force of CAs, in concert with the effect of glucocorticoids, might be a part of an important feedback mechanism (Fig. 1). Thus, an excessive immune response, through activation of the stress system, and hence, through glucocorticoids and Cas, suppresses the Th1 response and causes a Th2 shift. These beneficial effects may protect the organism from "overshooting" by type 1/pro-inflammatory cytokines and other products of activated macrophages with tissue damaging potential.

On the other hand, the substantial Th2-driving force of endogenous CAs can be amplified to a great extent during certain conditions such as severe *acute, subacute,* or *chronic stress*. For example, in major injury, a condition followed by a sympathetic storm, these effects of CAs may contribute to serious infectious complications. Therefore, a defect in the sympathetic-immune interface, or an abnormal activity of the SNS in either direction, might contribute at a certain point to the pathophysiology of common human diseases, where a selection of Th1 (type 1) versus Th2 (type 2) responses plays a significant role. These include several infections, major injury and its complications, allergic (atopic) reactions, autoimmune/inflammatory diseases, and tumor growth.

Locally, as stated above, the SNS may exert pro- or anti-inflammatory effects. This may be influenced by several factors, such as the presence or absence of antigen, the nature of antigen, and/or the presence and relative expression of particular receptor subtypes on

the surface of immune cells (e.g., β_2- versus α_2-adrenergic receptors), the type of G-protein coupled to the β_2-AR (e.g., G_s versus G_i), the stage of activation/differentiation of the cell, or the presence or absence of a particular receptor (e.g., β_2-ARs on Th1 but not on Th2 cells). Thus, the precise mapping and type of adrenoreceptor expression on different lymphoid cells and their coupling to intracellular pathways, according to their stage of maturation, differentiation, and tissue localization, clearly need further studies. This may provide new tools for pharmacologic tailoring of inflammatory conditions.

In summary, the immune system is not autonomous; the SNS and HPA axis may represent the major communication channels through which the CNS superimposes its control on the immune system. Better knowledge and understanding of the physiology and pathophysiology of the sympathetic-immune interface may help the development of new therapeutic strategies for common human diseases. Thus, blocking the effects of SNS or stress by β_2-AR antagonists or administration of α_2-AR agonists (used as antihypertensive drugs) may result in the boosting of Th1 responses that may be useful in the management of certain intracellular infections or tumors. The administration of β_2-AR agonists, α_2-AR antagonists, and/or selective inhibitors of PDEIV may help in the management of Th1-mediated autoimmune diseases, such as RA and MS. In addition, α_2-AR-antagonists able to increase noradrenergic activity might have therapeutic benefits in the treatment of fibromyalgia and chronic fatigue syndrome.

REFERENCES

Abadie C, Foucart S, Page P and Nadeau R (1997) Interleukin-1 beta and tumor necrosis factor-alpha inhibit the release of [3H]-noradrenaline from isolated human atrial appendages. *Naunyn Schmiedebergs Arch Pharmacol* **355**:384–389.

Abbas AK, Murphy KM and Sher A (1996) Functional diversity of helper T lymphocytes. *Nature (Lond)* **383**:787–793.

Ackerman KD, Felten SY, Bellinger DL and Felten DL (1987) Noradrenergic sympathetic innervation of the spleen: III. Development of innervation in the rat spleen. *J Neurosci Res* **18**:49–54.

Ackerman KD, Madden KS, Livnat S, Felten SY and Felten DL (1991) Neonatal sympathetic denervation alters the development of in vitro spleen cell proliferation and differentiation. *Brain Behav Immun* **5**:235–261.

Ader R and Cohen N (1982) Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science (Wash DC)* **215**:1534–1536.

Aloe L (1998) Nerve growth factor and autoimmune diseases: Role of tumor necrosis factor-alpha? *Adv Pharmacol* **42**:591–594.

Aloe L, Bracci-Laudiero L, Bonini S and Manni L (1997) The expanding role of nerve growth factor from neurotrophic activity to immunologic diseases. *Allergy* **52**:883–894.

Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le Deist F, Drysdale P, Jouanguy E, Doffinger R, Bernaudin F, Jeppsson O, Gollob JA, Meinl E, Segal AW, Fischer A, Kumararatne D and Casanova JL (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science(Wash DC)* **280**: 1432–1435.

Anastassiou ED, Paliogianni F, Balow JP, Yamada H and Boumpas DT (1992) Prostaglandin E2 and other cyclic AMP-elevating agents modulate IL-2 and IL-2R alpha gene expression at multiple levels. *J Immunol* **148**:2845–2852.

Anderson DJ and Axel R (1986) A bipotential neuroendocrine precursor whose choice of cell fate is determined by NGF and glucocorticoids. *Cell* **47**:1079–1090.

Arnason BG, Noronha AB and Reder AT (1988) Immunoregulation in rapidly progressive multiple sclerosis. *Ann N Y Acad Sci* **540**:4–12.

Awatsuji H, Furukawa Y, Hirota M, Murakami Y, Nii S, Furukawa S and Hayashi K (1993) Interleukin-4 and -5 as modulators of nerve growth factor synthesis/secretion in astrocytes. *J Neurosci Res* **34**:539–545.

Baerwald CG, Laufenberg M, Specht T, von Wichert P, Burmester GR and Krause A (1997) Impaired sympathetic influence on the immune response in patients with rheumatoid arthritis due to lymphocyte subset-specific modulation of beta 2-adrenergic receptors. *Br J Rheumatol* **36**:1262–1269.

Baker AJ and Fuller RW (1995) Loss of response to beta-adrenoceptor agonists during the maturation of human monocytes to macrophages in vitro. *J Leukocyte Biol* **57**:395–400.

Barnett CCJ, Moore EE, Partrick DA and Silliman CC (1997) Beta-adrenergic stimulation down-regulates neutrophil priming for superoxide generation, but not elastase release. *J Surg Res* **70**:166–170.

Bartik MM, Brooks WH and Roszman TL (1993) Modulation of T cell proliferation by stimulation of the beta-adrenergic receptor: Lack of correlation between inhibition of T cell proliferation and cAMP accumulation. *Cell Immunol* **148**:408–421.

Bellinger DL, Felten SY, Collier TJ and Felten DL (1987) Noradrenergic sympathetic innervation of the spleen: IV. Morphometric analysis in adult and aged F344 rats. *J Neurosci Res* **18**:55–59.

Bellinger DL, Felten SY and Felten DL (1988) Maintenance of noradrenergic sympathetic innervation in the involuted thymus of the aged Fischer 344 rat. *Brain Behav Immun* **2**:133–150.

Bellinger DL, Lorton D, Felten SY and Felten DL (1992) Innervation of lymphoid organs and implications in development, aging, and autoimmunity. *Int J Immunopharmacol* **14**:329–344.

Bencsics A, Elenkov IJ and Vizi ES (1997a) Effect of morphine on lipopolysaccharide-induced tumor necrosis factor-alpha production in vivo: Involvement of the sympathetic nervous system. *J Neuroimmunol* **73**:1–6.

Bencsics A, Sershen H, Baranyi M, Hashim A, Lajtha A and Vizi ES (1997b) Dopamine, as well as norepinephrine, is a link between noradrenergic nerve terminals and splenocytes. *Brain Res* **761**:236–243.

Bender BS, Bell WE, Taylor S and Scarpace PJ (1993) Decreased sensitivity to cAMP in the in vitro generation of memory splenic cytotoxic T-lymphocytes from aged mice: Role of phosphodiesterase. *J Pharmacol Exp Ther* **264**:1381–1386.

Benschop RJ, Oostveen FG, Heijnen CJ and Ballieux RE (1993) Beta 2-adrenergic stimulation causes detachment of natural killer cells from cultured endothelium. *Eur J Immunol* **23**:3242–3247.

Benschop RJ, Rodriguez-Feuerhahn M and Schedlowski M (1996) Catecholamine-induced leukocytosis: Early observations, current research, and future directions. *Brain Behav Immun* **10**:77–91.

Berkenbosch F, de Goeij Dec, del Rey AE and Besedovsky HO (1989) Neuroendocrine, sympathetic and metabolic responses induced by interleukin-1. *Neuroendocrinology* **50**:570–576.

Berkenbosch F, van Oers J, del Rey A, Tilders F and Besedovsky H (1987) Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science (Wash DC)* **238**:524–526.

Bermudez LE, Wu M and Young LS (1990) Effect of stress-related hormones on macrophage receptors and response to tumor necrosis factor. *Lymphokine Res* **9**:137–145.

Besedovsky HO, del Rey A, Sorkin E, Da Prada M and Keller HH (1979) Immunoregulation mediated by the sympathetic nervous system. *Cell Immunol* **48**:346–355.

Besedovsky HO, del Rey A, Sorkin E and Dinarello CA (1986) Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science (Wash DC)* **233**:652–654.

Besedovsky HO, del Rey AE and Sorkin E (1981) Lymphokine-containing supernatants from Con A-stimulated cells increase corticosterone blood levels. *J Immunology* **126**:385–389.

Besedovsky HO, del Rey AE, Sorkin E, Da Prada M, Burri R and Honegger C (1983) The immune response evokes changes in brain noradrenergic neurons. *Science (Wash DC)* **221**:564–566.

Besedovsky HO, Sorkin E, Keller M and Muller J (1975) Changes in blood hormone levels during the immune response. *Proc Soc Exp Biol Med* **150**:466–470.

Bienenstock J, Croitoru K, Ernst PB and Stanisz AM (1989) Nerves and neuropeptides in the regulation of mucosal immunity. *Adv Exp Med Biol* **257**:19–26.

Bischoff SC and Dahinden CA (1992) Effect of nerve growth factor on the release of inflammatory mediators by mature human basophils. *Blood* **79**:2662–2669.

Bismuth G, Theodorou I, Gouy H, Le Gouvello S, Bernard A and Debre P (1988) Cyclic AMP-mediated alteration of the CD2 activation process in human T lymphocytes. Preferential inhibition of the phosphoinositide cycle-related transduction pathway. *Eur J Immunol* **18**:1351–1357.

Bissonnette EY and Befus AD (1997) Anti-inflammatory effect of beta 2-agonists: Inhibition of TNF-alpha release from human mast cells. *J Allergy Clin Immunol* **100**:825–831.

Blandizzi C, Tarkovacs G, Natale G, Del Tacca M and Vizi ES (1993) Functional evidence that [^{3}H]acetylcholine and [^{3}H]noradrenaline release from guinea pig ileal myenteric plexus and noradrenergic terminals is modulated by different presynaptic alpha-2 adrenoceptor subtypes. *J Pharmacol Exp Ther* **267**:1054–1060.

Blennerhassett MG and Bienenstock J (1998) Sympathetic nerve contact causes maturation of mast cells *in vitro*. *J Neurobiol* **35**:173–182.

Bondy B, de Jonge S, Pander S, Primbs J and Ackenheil M (1996) Identification of dopamine D4 receptor mRNA in circulating human lymphocytes using nested polymerase chain reaction. *J Neuroimmunol* **71**:139–144.

Bonini S, Lambiase A, Levi-Schaffer F and Aloe L (1999) Nerve growth factor: An important molecule in allergic inflammation and tissue remodelling. *Int Arch Allergy Immunol* **118**:159–162.

Borger P, Hoekstra Y, Esselink MT, Postma DS, Zaagsma J, Vellenga E and Kauffman HF (1998) Beta-adrenoceptor-mediated inhibition of IFN-gamma, IL-3, and GM-CSF mRNA accumulation in activated human T lymphocytes is solely mediated by the beta2-adrenoceptor subtype. *Am J Respir Cell Mol Biol* **19**:400–407.

Borger P, Kauffman HF, Vijgen JL, Postma DS and Vellenga E (1996) Activation of the cAMP-dependent signaling pathway downregulates the expression of interleukin-3 and granulocyte-macrophage colony-stimulating factor in activated human T lymphocytes. *Exp Hematol* **24**:108–115.

Bornstein SR and Vaudry H (1998) Paracrine and neuroendocrine regulation of the adrenal gland—basic and clinical aspects. *Horm Metab Res* **30**:292–296.

Braun A, Appel E, Baruch R, Herz U, Botchkarev V, Paus R, Brodie C and Renz H (1998) Role of nerve growth factor in a mouse model of allergic airway inflammation and asthma. *Eur J Immunol* **28**:3240–3251.

Brodie C (1996) Differential effects of Th1 and Th2 derived cytokines on NGF synthesis by mouse astrocytes. *FEBS Lett* **394**:117–120.

Brown JE and Adamson JW (1977) Modulation of in vitro erythropoiesis. The influence of beta-adrenergic agonists on erythroid colony formation. *J Clin Invest* **60**:70–77.

Brown R, Li Z, Vriend CY, Nirula R, Janz L, Falk J, Nance DM, Dyck DG and Greenberg AH (1991) Suppression of splenic macrophage interleukin-1 secretion following intracerebroventricular injection of interleukin-1: Evidence for pituitary-adrenal and sympathetic control. *Cell Immunol* **132**:84–93.

Brune IB, Wilke W, Hensler T, Holzmann B and Siewert Jr (1999) Downregulation of T helper type 1 immune response and altered pro-inflammatory and anti-inflammatory T cell cytokine balance following conventional but not laparoscopic surgery. *Am J Surg* **177**:55–60.

Bulloch K and Pomerantz W (1984) Autonomic nervous system innervation of thymic-related lymphoid tissue in wildtype and nude mice. *J Comp Neurol* **228**:57–68.

Bullock ED and Johnson Emj (1996) Nerve growth factor induces the expression of certain cytokine genes and bcl-2 in mast cells. Potential role in survival promotion. *J Biol Chem* **271**:27500–27508.

Burysek L and Houstek J (1997) Beta-Adrenergic stimulation of interleukin-1alpha and interleukin-6 expression in mouse brown adipocytes. *FEBS Lett* **411**:83–86.

Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, Molinoff PB, Ruffolo RR and Trendelenburg AU (1994) IV. International Union of Pharmacology nomenclature of adrenoceptors. *Pharmacol Rev* **46**:121–126.

Byron JW (1971) Evidence for a α_2-adrenergic receptor initiating DNA synthesis in haemopoetic stem cells. *Exp Cell Res* 228–232.

Calvo W and Haas RJ (1969) On the histogenesis of the bone marrow in the rat. Innervation, stroma and their relations to hemopoiesis. *Z Zellforsch Mikrosk Anat* **95**:377–395.

Carlson SL, Brooks WH and Roszman TL (1989a) Neurotransmitter-lymphocyte interactions: Dual receptor modulation of lymphocyte proliferation and cAMP production. *J Neuroimmunol* **24**:155–162.

Carlson SL and Felten DL (1989b) Involvement of hypothalamic and limbic structures in neural-immune communication, in *Neuroimmune Networks: Physiology and Diseases* (Goetzl EJ and Spector NH eds) pp 219–226, Alan R. Liss, Inc., New York.

Carlson SL, Trauth K, Brooks WH and Roszman TL (1994) Enhancement of beta-adrenergic-induced cAMP accumulation in activated T-cells. *J Cell Physiol* **161**: 39–48.

Carpenter GH, Garrett JR, Hartley RH and Proctor GB (1998) The influence of nerves on the secretion of immunoglobulin A into submandibular saliva in rats. *J Physiol (Lond)* **512**:567–573.

Casale TB and Kaliner M (1984) Demonstration that circulating human blood cells have no detectable alpha 1-adrenergic receptors by radioligand binding analysis. *J Allergy Clin Immunol* **74**:812–818.

Cavallotti C, Artico N and Cavallotti D (1999) Occurrence of adrenergic nerve fibers and of noradrenaline in thymus gland of juvenile and aged rats. *Immunol Lett* **70**:53–62.

Cazaux CA, Sterin-Borda L, Gorelik G and Cremaschi GA (1995) Down-regulation of beta-adrenergic receptors induced by mitogen activation of intracellular signaling events in lymphocytes. *FEBS Lett* **364**:120–124.

Chambers DA, Cohen RL and Perlman RL (1993) Neuroimmune modulation: Signal transduction and catecholamines. *Neurochem Int* **22**:95–110.

Chan SC, Grewe SR, Stevens SR and Hanifin JM (1982) Functional desensitization due to stimulation of cyclic AMP-phosphodiesterase in human mononuclear leukocytes. *J Cyclic Nucleotide Res* **8**:211–224.

Charon I, Zuin-Kornmann G, Bataille S and Schorderet M (1998) Protective effect of neurotrophic factors, neuropoietic cytokines and dibutyryl cyclic AMP on hydrogen peroxide-induced cytotoxicity on PC12 cells: A possible link with the state of differentiation. *Neurochem Int* **33**:503–511.

Chelmicka-Schorr E, Checinski M and Arnason BG (1988) Chemical sympathectomy augments the severity of experimental allergic encephalomyelitis. *J Neuroimmunol* **17**:347–350.

Chelmicka-Schorr E, Kwasniewski MN, Thomas BE and Arnason BG (1989) The beta-adrenergic agonist isoproterenol suppresses experimental allergic encephalomyelitis in Lewis rats. *J Neuroimmunol* **25**:203–207.

Chen D and Rothenberg EV (1994) Interleukin 2 transcription factors as molecular targets of cAMP inhibition: Delayed inhibition kinetics and combinatorial transcription roles. *J Exp Med* **179**:931–942.

Chen WF, Fischer M, Frank G and Zlotnik A (1989) Distinct patterns of lymphokine requirement for the proliferation of various subpopulations of activated thymocytes in a single cell assay. *J Immunol* **143**:1598–1605.

Chiolero R and Berger M (1994) Endocrine response to brain injury. *New Horiz* **2**:432–442.

Chou RC, Stinson MW, Noble BK and Spengler RN (1996) Beta-adrenergic receptor regulation of macrophage-derived tumor necrosis factor-alpha production from rats with experimental arthritis. *J Neuroimmunol* **67**:7–16.

Chouaib S, Asselin-Paturel C, Mami-Chouaib F, Caignard A and Blay JY (1997) The host-tumor immune conflict: From immunosuppression to resistance and destruction. *Immunol Today* **18**:493–497.

Chouaib S, Welte K, Mertelsmann R and Dupont B (1985) Prostaglandin E2 acts at two distinct pathways of T lymphocyte activation: Inhibition of interleukin 2 production and down-regulation of transferrin receptor expression. *J Immunol* **135**:1172–1179.

Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* **332**:1351–1362.

Chrousos GP and Gold PW (1992) The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis [published erratum appears in *JAMA* (1992) 268:200]. *JAMA* **267**:1244–1252.

Chuang TT, Iacovelli L, Sallese M and De Blasi A (1996) G protein-coupled receptors: Heterologous regulation of homologous desensitization and its implications. *Trends Pharmacol Sci* **17**:416–421.

Church MK, el-Lati S and Caulfield JP (1991) Neuropeptide-induced secretion from human skin mast cells. *Int Arch Allergy Appl Immunol* **94**:310–318.

Clauw DJ and Chrousos GP (1997) Chronic pain and fatigue syndromes: Overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation* **4**:134–153.

Clauw DJ, Radulovic D, Antonetti D, Bagati R, Baraniuk J and Barbey JT (1996a) Tilt table tasting in fibromyalgia. *Arthritis Rheum* **39(9S)**:S276.

Clauw DJ, Radulovic D, Heshmat Y and Barbey JT (1996b) Heart rate variability as a measure of autonomic dysfunction in patients with fibromyalgia. *Arthritis Rheum* **39(9S)**:S276.

Cohen S, Tyrrell DA and Smith AP (1991) Psychological stress and susceptibility to the common cold. *N Engl J Med* **325**:606–612.

Cohen WR, Galen LH, Vega-Rich M and Young JB (1988) Cardiac sympathetic activity during rat pregnancy. *Metabolism* **37**:771–777.

Cole SW, Korin YD, Fahey JL and Zack JA (1998) Norepinephrine accelerates HIV replication via protein kinase A-dependent effects on cytokine production. *J Immunol* **161**:610–616.

Cole TJ, Blendy JA, Monaghan AP, Krieglstein K, Schmid W, Aguzzi A, Fantuzzi G, Hummler E, Unsicker K and Schutz G (1995) Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. *Genes Dev* **9**:1608–1621.

Colombo MP, Vagliani M, Spreafico F, Parenza M, Chiodoni C, Melani C and Stoppacciaro A (1996) Amount of interleukin 12 available at the tumor site is critical for tumor regression. *Cancer Res* **56**:2531–2534.

Cooke HJ (1986) Neurobiology of the intestinal mucosa. *Gastroenterology* **90**:1057–1081.

Cook-Mills JM, Mokyr MB, Cohen RL, Perlman RL and Chambers DA (1995) Neurotransmitter suppression of the in vitro generation of a cytotoxic T lymphocyte response against the syngeneic MOPC-315 plasmacytoma. *Cancer Immunol Immunother* **40**:79–87.

Coqueret O, Dugas B, Mencia-Huerta JM and Braquet P (1995) Regulation of IgE production from human mononuclear cells by beta 2-adrenoceptor agonists. *Clin Exp Allergy* **25**:304–311.

Coqueret O, Lagente V, Frere CP, Braquet P and Mencia-Huerta JM (1994a) Regulation of IgE production by beta 2-adrenoceptor agonists. *Ann N Y Acad Sci* **725**:44–49.

Cruz-Aguado R, Francis-Turner L, Diaz-Suarez CM and Bergado J (1999) NGF prevents changes in rat brain glutathione-related enzymes following transection of the septohippocampal pathway. *Neurochem Int* **34**:125–130.

Culmsee C, Semkova I and Krieglstein J (1999) NGF mediates the neuroprotective effect of the beta2-adrenoceptor agonist clenbuterol in vitro and in vivo: Evidence from an NGF-antisense study. *Neurochem Int* **35**:47–57.

Cunha FQ, Lorenzetti BB, Poole S and Ferreira SH (1991) Interleukin-8 as a mediator of sympathetic pain. *Br J Pharmacol* **104**:765–767.

Daaka Y, Luttrell LM and Lefkowitz RJ (1997) Switching of the coupling of the beta2-adrenergic receptor to different G proteins by protein kinase A. *Nature (Lond)* **390**:88–91.

Dahlström AB and Zetterström BEM (1965) Noradrenaline stores in nerve terminals of the spleen: Changes during hemorrhagic shock. *Science (Wash DC)* **147**:1583–1585.

De Blasi BA, Parruti G and Sallese M (1995) Regulation of G protein-coupled receptor kinase subtypes in activated T lymphocytes. Selective increase of beta-adrenergic receptor kinase 1 and 2. *J Clin Invest* **95**:203–210.

DeCoursey TE, Chandy KG, Gupta S and Cahalan MD (1984) Voltage-gated K+ channels in human T lymphocytes: A role in mitogenesis? *Nature (Lond)* **307**:465–468.

Delgado M, Sun W, Leceta J and Ganea D (1999) VIP and PACAP differentially regulate the costimulatory activity of resting and activated macrophages through the modulation of B7.1 and B7.2 expression. *J Immunol* **163**:4213–4223.

Del Rey A, Besedovsky HO, Sorkin E, Da Prada M and Bondiolotti GP (1982) Sympathetic immunoregulation: Difference between high and low-responder animals. *Am J Physiol* **242**:R30–R33.

DeRijk RH, Boelen A, Tilders FJ and Berkenbosch F (1994) Induction of plasma interleukin-6 by circulating adrenaline in the rat. *Psychoneuroendocrinology* **19**: 155–163.

Ding M, Hart RP and Jonakait GM (1995) Tumor necrosis factor-alpha induces substance P in sympathetic ganglia through sequential induction of interleukin-1 and leukemia inhibitory factor. *J Neurobiol* **28**:445–454.

Docherty JR (1998) Subtypes of functional alpha1- and alpha2-adrenoceptors. *Eur J Pharmacol* **361**:1–15.

Dougherty TF and Frank JA (1953) The quantitative and qualitative responses of blood lymphocytes to stress stimuli. *J Lab Clin Med* **42**:530–537.

Dunn AJ (1998a) Brain catecholaminergic and tryptophan responses to restraint are attenuated by nitric oxide synthase inhibition. *Neurochem Int* **33**:551–557.

Dunn AJ (1988b) Systemic interleukin-1 administration stimulates hypothalamic norepinephrine metabolism parallelling the increased plasma corticosterone. *Life Sci* **43**:429–435.

Dunn AJ, Wang J and Ando T (1999) Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv Exp Med Biol* **461**:117–127.

Ehrenstrom F and Ungell AL (1990) Nerve impulse-induced release of endogenous noradrenaline and adrenaline from the perfused cod spleen. *J Comp Physiol [B]* **160**:401–406.

Ehring GR, Kerschbaum HH, Eder C, Neben AL, Fanger CM, Khoury RM, Negulescu PA and Cahalan MD (1998) A nongenomic mechanism for progesterone-mediated immunosuppression: Inhibition of K+ channels, Ca2+ signaling, and gene expression in T lymphocytes. *J Exp Med* **188**:1593–1602.

Eigler A, Sinha B, Hartmann G and Endres S (1997) Taming TNF: Strategies to restrain this proinflammatory cytokine. *Immunol Today* **18**:487–492.

Elam M, Johansson G and Wallin BG (1992) Do patients with primary fibromyalgia have an altered muscle sympathetic nerve activity? *Pain* **48**:371–375.

Elenkov IJ (1993) Interface role of noradrenergic innervation in neuro-immune communication. *Ph D thesis*.
Elenkov IJ and Chrousos GP (1999) Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends Endocrinol Metab* **10**:359–368.
Elenkov IJ, Hasko G, Kovacs KJ and Vizi ES (1995) Modulation of lipopolysaccharide-induced tumor necrosis factor-alpha production by selective alpha- and beta-adrenergic drugs in mice. *J Neuroimmunol* **61**:123–131.
Elenkov IJ, Hoffman J and Wilder RL (1997) Does differential neuroendocrine control of cytokine production govern the expression of autoimmune diseases in pregnancy and the postpartum period? *Mol Med Today* **3**:379–383.
Elenkov IJ, Kovacs K, Duda E, Stark E and Vizi ES (1992a) Presynaptic inhibitory effect of TNF-alpha on the release of noradrenaline in isolated median eminence. *J Neuroimmunol* **41**:117–120.
Elenkov IJ, Kovacs K, Kiss J, Bertok L and Vizi ES (1992b) Lipopolysaccharide is able to bypass corticotrophin-releasing factor in affecting plasma ACTH and corticosterone levels: Evidence from rats with lesions of the paraventricular nucleus. *J Endocrinol* **133**:231–236.
Elenkov IJ, Papanicolaou DA, Wilder RL and Chrousos GP (1996) Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: Clinical implications. *Proc Assoc Am Physicians* **108**:374–381.
Elenkov IJ and Vizi ES (1991) Presynaptic modulation of release of noradrenaline from the sympathetic nerve terminals in the rat spleen. *Neuropharmacology* **30**:1319–1324.
Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP and Wilder RL (1998) Histamine potently suppresses human IL-12 and stimulates IL-10 production via H2 receptors. *J Immunol* **161**:2586–2593.
Elenkov IJ, Webster EL, Torpy DJ and Chrousos GP (1999) Stress, corticotropin-releasing hormone, glucocorticoids, and the immune/inflammatory response: Acute and chronic effects. *Ann N Y Acad Sci* **876**:1–13.
Elliott L, Brooks W and Roszman T (1992) Inhibition of anti-CD3 monoclonal antibody-induced T-cell proliferation by dexamethasone, isoproterenol, or prostaglandin E2 either alone or in combination. *Cell Mol Neurobiol* **12**:411–427.
Engstad CS, Lund T and Osterud B (1999) Epinephrine promotes IL-8 production in human leukocytes via an effect on platelets. *Thromb Haemostasis* **81**:139–145.
Ernst PB, Song F, Klimpel GR, Haeberle H, Bamford KB, Crowe SE, Ye G and Reyes VE (1999) Regulation of the mucosal immune response. *Am J Trop Med Hyg* **60**:2–9.
Fabian TC, Croce MA, Fabian MJ, Trenthem LL, Yockey JM, Boscarino R and Proctor KG (1995) Reduced tumor necrosis factor production in endotoxin-spiked whole blood after trauma: Experimental results and clinical correlation. *Surgery* **118**:63–72.
Fearon DT and Locksley RM (1996) The instructive role of innate immunity in the acquired immune response. *Science (Wash DC)* **272**:50–53.
Fecho K, Dykstra LA and Lysle DT (1993) Evidence for beta adrenergic receptor involvement in the immunomodulatory effects of morphine. *J Pharmacol Exp Ther* **265**:1079–1087.
Fecho K, Maslonek KA, Dykstra LA and Lysle DT (1996) Evidence for sympathetic and adrenal involvement in the immunomodulatory effects of acute morphine treatment in rats. *J Pharmacol Exp Ther* **277**:633–645.
Fedyk ER, Adawi A, Looney RJ and Phipps RP (1996) Regulation of IgE and cytokine production by cAMP: Implications for extrinsic asthma. *Clin Immunol Immunopathol* **81**:101–113.
Feldman RD, Hunninghake GW and McArdle WL (1987) Beta-adrenergic-receptor-mediated suppression of interleukin 2 receptors in human lymphocytes. *J Immunol* **139**:3355–3359.
Felten DL, Felten SY, Bellinger DL and Lorton D (1992) Noradrenergic and peptidergic innervation of secondary lymphoid organs: Role in experimental rheumatoid arthritis. *Eur J Clin Invest* **22 (Suppl 1)**:37–41.
Felten DL, Felten SY, Carlson SL, Olschowka JA and Livnat S (1985) Noradrenergic and peptidergic innervation of lymphoid tissue. *J Immunol* **135**:755s–765s.
Felten DL, Livnat S, Felten SY, Carlson SL, Bellinger DL and Yeh P (1984) Sympathetic innervation of lymph nodes in mice. *Brain Res Bull* **13**:693–699.
Felten SY, Felten DL, Bellinger DL, Carlson SL, Ackerman KD, Madden KS, Olschowka JA and Livnat S (1988) Noradrenergic sympathetic innervation of lymphoid organs. *Prog Allergy* **43**:14–36.
Felten SY and Olschowka J (1987) Noradrenergic sympathetic innervation of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminals form synaptic-like contacts on lymphocytes in the splenic white pulp. *J Neurosci Res* **18**:37–48.
Fink GD and Fisher JW (1977) Stimulation of erythropoiesis by beta adrenergic agonists. I. Characterization of activity in polycythemic mice. *J Pharmacol Exp Ther* **202**:192–198.
Fink T and Weihe E (1988) Multiple neuropeptides in nerves supplying mammalian lymph nodes: Messenger candidates for sensory and autonomic neuroimmunomodulation? *Neurosci Lett* **90**:39–44.
Fisher DA, Hoath S and Lakshmanan J (1982) The thyroid hormone effects on growth and development may be mediated by growth factors. *Endocrinol Exp* **16**:259–271.
Fisher SA and Absher M (1995) Norepinephrine and ANG II stimulate secretion of TGF-beta by neonatal rat cardiac fibroblasts in vitro. *Am J Physiol* **268**:C910–C917.
Foreman JC (1987) Substance P and calcitonin gene-related peptide: Effects on mast cells and in human skin. *Int Arch Allergy Appl Immunol* **82**:366–371.
Foucart S and Abadie C (1996) Interleukin-1 beta and tumor necrosis factor-alpha inhibit the release of [^{3}H]-noradrenaline from mice isolated atria. *Naunyn Schmiedebergs Arch Pharmacol* **354**:1–6.
Furness JB and Costa M (1980) Types of nerves in the enteric nervous system. *Neuroscience* **5**:1–20.
Gaddis RR and Dixon WR (1982) Presynaptic opiate receptor-mediated inhibition of endogenous norepinephrine and dopamine-beta-hydroxylase release in the cat spleen, independent of the presynaptic alpha adrenoceptors. *J Pharmacol Exp Ther* **223**:77–83.
Genain CP, Roberts T, Davis RL, Nguyen MH, Uccelli A, Faulds D, Li Y, Hedgpeth J and Hauser SL (1995) Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase inhibitor. *Proc Natl Acad Sci USA* **92**:3601–3605.
Gibson-Berry KL, Whitin JC and Cohen HJ (1993) Modulation of the respiratory burst in human neutrophils by isoproterenol and dibutyryl cyclic AMP. *J Neuroimmunol* **43**:59–68.
Giron LTJ, Crutcher KA and Davis JN (1980) Lymph nodes–a possible site for sympathetic neuronal regulation of immune responses. *Ann Neurol* **8**:520–525.
Grant KR, Harnett W, Milligan G and Harnett MM (1997) Differential G-protein expression during B- and T-cell development. *Immunology* **90**:564–571.
Green PG, Luo J, Heller PH and Levine JD (1994) Effect of E-type prostaglandins on bradykinin-induced plasma extravasation in the knee joint of the rat. *Eur J Pharmacol* **252**:127–132.
Green PG, Miao FJ, Strausbaugh H, Heller P, Janig W and Levine JD (1998) Endocrine and vagal controls of sympathetically dependent neurogenic inflammation. *Ann N Y Acad Sci* **840**:282–288.
Grohmann U, van Snick J, Campanile F, Silla S, Giampietri A, Vacca C, Renauld J-C, Fioretti MC and Puccetti P (2000) IL-9 protects mice from Gram-negative bacterial shock: Suppression of TNF-α, IL-12 and IFN-γ and induction of IL-10. *J Immunol* **164**:4197–4203.
Hadcock JR, Wang HY and Malbon CC (1989) Agonist-induced destabilization of beta-adrenergic receptor mRNA. Attenuation of glucocorticoid-induced up-regulation of beta-adrenergic receptors. *J Biol Chem* **264**:19928–19933.
Hadden JW, Hadden EM and Middleton E Jr (1970) Lymphocyte blast transformation. I. Demonstration of adrenergic receptors in human peripheral lymphocytes. *Cell Immunol* **1**:583–595.
Haraguchi S, Good RA and Day NK (1995a) Immunosuppressive retroviral peptides: cAMP and cytokine patterns. *Immunol Today* **16**:595–603.
Haraguchi S, Good RA, James-Yarish M, Cianciolo GJ and Day NK (1995b) Differential modulation of Th1- and Th2-related cytokine mRNA expression by a synthetic peptide homologous to a conserved domain within retroviral envelope protein [published erratum appears in *Proc Natl Acad Sci USA* (1995) **92**:9009]. *Proc Natl Acad Sci USA* **92**:3611–3615.
Haraguchi S, Good RA, James-Yarish M, Cianciolo GJ and Day NK (1995c) Induction of intracellular cAMP by a synthetic retroviral envelope peptide: A possible mechanism of immunopathogenesis in retroviral infections. *Proc Natl Acad Sci USA* **92**:5568–5571.
Harvath L, Robbins JD, Russell AA and Seamon KB (1991) cAMP and human neutrophil chemotaxis. Elevation of cAMP differentially affects chemotactic responsiveness. *J Immunol* **146**:224–232.
Hasko G, Elenkov IJ, Kvetan V and Vizi ES (1995a) Differential effect of selective block of alpha 2-adrenoreceptors on plasma levels of tumour necrosis factor-alpha, interleukin-6 and corticosterone induced by bacterial lipopolysaccharide in mice. *J Endocrinol* **144**:457–462.
Hasko G, Elenkov IJ and Vizi ES (1995b) Presynaptic receptors involved in the modulation of release of noradrenaline from the sympathetic nerve terminals of the rat thymus. *Immunol Lett* **47**:133–137.
Hasko G, Nemeth ZH, Szabo C, Zsilla G, Salzman AL and Vizi ES (1998a) Isoproterenol inhibits Il-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages. *Brain Res Bull* **45**:183–187.
Hasko G, Shanley TP, Egnaczyk G, Nemeth ZH, Salzman AL, Vizi ES and Szabo C (1998b) Exogenous and endogenous catecholamines inhibit the production of macrophage inflammatory protein (MIP) 1 alpha via a beta adrenoceptor mediated mechanism. *Br J Pharmacol* **125**:1297–1303.
Hasko G, Szabo C, Merkel K, Bencsics A, Zingarelli B, Kvetan V and Vizi ES (1996a) Modulation of lipopolysaccharide-induced tumor necrosis factor-alpha and nitric oxide production by dopamine receptor agonists and antagonists in mice. *Immunol Lett* **49**:143–147.
Hasko G, Szabo C, Nemeth ZH, Kvetan V, Pastores SM and Vizi ES (1996b) Adenosine receptor agonists differentially regulate IL-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice. *J Immunol* **157**:4634–4640.
Hasko G, Szabo C, Nemeth ZH, Lendvai B and Vizi ES (1998c) Modulation by dantrolene of endotoxin-induced interleukin-10, tumour necrosis factor-alpha and nitric oxide production in vivo and in vitro. *Br J Pharmacol* **124**:1099–1106.
Hasko G, Szabo C, Nemeth ZH, Salzman AL and Vizi ES (1998d) Stimulation of beta-adrenoceptors inhibits endotoxin-induced IL-12 production in normal and IL-10 deficient mice. *J Neuroimmunol* **88**:57–61.
Hasko G, Szabo C, Nemeth ZH, Salzman AL and Vizi ES (1998e) Suppression of IL-12 production by phosphodiesterase inhibition in murine endotoxemia is IL-10 independent. *Eur J Immunol* **28**:468–472.
Hatfield SM, Petersen BH and DiMicco JA (1986) Beta adrenoceptor modulation of the generation of murine cytotoxic T lymphocytes in vitro. *J Pharmacol Exp Ther* **239**:460–466.
Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ and Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* **330**:1717–1722.
Heesen M, Deinsberger W, Dietrich GV, Detsch O, Boldt J and Hempelmann G (1996) Increase of interleukin-6 plasma levels after elective craniotomy: Influence of interleukin-10 and catecholamines. *Acta Neurochir (Wien)* **138**:77–80.
Heijnen CJ, Rouppe van der Voort C, Wulffraat N, van der Net J, Kuis W and Kavelaars A (1996) Functional alpha 1-adrenergic receptors on leukocytes of patients with polyarticular juvenile rheumatoid arthritis. *J Neuroimmunol* **71**: 223–226.
Heilig M, Irwin M, Grewal I and Sercarz E (1993) Sympathetic regulation of T-helper cell function. *Brain Behav Immun* **7**:154–163.
Hein L, Limbird LE, Eglen RM and Kobilka BK (1998) Gene substitution/knockout

to delineate the role of α2-adrenoceptor subtypes in mediating central effects of catecholamine and imidazoles. *Ann NY Acad Sci* **881**:265–270.
Hellstrand K and Hermodsson S (1989) An immunopharmacological analysis of adrenaline-induced suppression of human natural killer cell cytotoxicity. *Int Arch Allergy Appl Immunol* **89**:334–341.
Hensler T, Heidecke C, Hecker H, Heeg K, Bartels H, Zantl N, Wagner H, Siewert J and Holzmann B (1998) Increased susceptibility to postoperative sepsis in patients with impaired monocyte IL-12 production. *J Immunol* **161**:2655–2659.
Herrmann E, Gierschik P and Jakobs KH (1989) Neomycin induces high-affinity agonist binding of G-protein-coupled receptors. *Eur J Biochem* **185**:677–683.
Hetier E, Ayala J, Bousseau A and Prochiantz A (1991) Modulation of interleukin-1 and tumor necrosis factor expression by beta-adrenergic agonists in mouse ameboid microglial cells. *Exp Brain Res* **86**:407–413.
Ho WZ, Stavropoulos G, Lai JP, Hu BF, Magafa V, Anagnostides S and Douglas SD (1998) Substance P C-terminal octapeptide analogues augment tumor necrosis factor-alpha release by human blood monocytes and macrophages. *J Neuroimmunol* **82**:126–132.
Horwitz DA, Gray JD, Behrendsen SC, Kubin M, Rengaraju M, Ohtsula K and Trinchieri G (1998) Decreased production of interleukin-12 and other Th1-type cytokines in patients with recent-onset systemic lupus erythematosus. *Arthritis Rheum* **41**:838–844.
Hotchkiss RS, Osborne DF, Lappas GD and Karl IE (1995) Calcium antagonists decrease plasma and tissue concentrations of tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-1 alpha in a mouse model of endotoxin. *Shock* **3**:337–342.
Hurst S and Collins SM (1993) Interleukin-1 beta modulation of norepinephrine release from rat myenteric nerves. *Am J Physiol* **264**:G30–G35.
Hurst SM and Collins SM (1994) Mechanism underlying tumor necrosis factor-alpha suppression of norepinephrine release from rat myenteric plexus. *Am J Physiol* **266**:G1123–G1129.
Ignatowski TA, Gallant S and Spengler RN (1996) Temporal regulation by adrenergic receptor stimulation of macrophage (M phi)-derived tumor necrosis factor (TNF) production post-LPS challenge. *J Neuroimmunol* **65**:107–117.
Ignatowski TA, Noble BK, Wright Jr, Gorfien JL, Heffner RR and Spengler RN (1997) Neuronal-associated tumor necrosis factor (TNF alpha): Its role in noradrenergic functioning and modification of its expression following antidepressant drug administration. *J Neuroimmunol* **79**:84–90.
Ignatowski TA and Spengler RN (1994) Tumor necrosis factor-alpha: Presynaptic sensitivity is modified after antidepressant drug administration. *Brain Res* **665**: 293–299.
Irwin M (1994) Stress-induced immune suppression: Role of brain corticotropin releasing hormone and autonomic nervous system mechanisms. *Adv Neuroimmunol* **4**:29–47.
Irwin M, Hauger R and Brown M (1992) Central corticotropin-releasing hormone activates the sympathetic nervous system and reduces immune function: Increased responsivity of the aged rat. *Endocrinology* **131**:1047–1053.
Ishida Y and Chused M (1993) Lack of voltage sensitive potassium channels and generation of membrane potential by sodium potassium ATPase in murine T lymphocytes. *J Immunol* **151**:610–620.
Ishigami T (1919) The influence of psychic acts on the progress of pulmonary tuberculosis. *Am Rev Tuberc* **2**:470–484.
Janig W and McLachlan EM (1992a) Characteristics of function-specific pathways in the sympathetic nervous system. *Trends Neurosci* **15**:475–481.
Janig W and McLachlan EM (1992b) Specialized functional pathways are the building blocks of the autonomic nervous system. *J Auton Nerv Syst* **41**:3–13.
Jarek MJ, Legare EJ, McDermott MT, Merenich JA and Kollef MH (1993) Endocrine profiles for outcome prediction from the intensive care unit. *Crit Care Med* **21**: 543–550.
Jensen BS, Odum N, Jorgensen NK, Christophersen P and Olesen SP (1999) Inhibition of T cell proliferation by selective block of Ca(2+)-activated K(+) channels. *Proc Natl Acad Sci USA* **96**:10917–10921.
Jonakait GM (1993) Neural-immune interactions in sympathetic ganglia. *Trends Neurosci* **16**:419–423.
Kable JW, Murrin C and Bylund DB (2000) In vivo gene modification elucidates subtype-specific functions of α2-adrenergic receptors. *J Pharmacol Exp Ther* **293**: 1–7.
Kaliner M, Orange RP and Austen KF (1972) Immunological release of histamine and slow reacting substance of anaphylaxis from human lung. IV Enhancement of cholinergic and alpha adrenergic stimulation. *J Exp Med* **136**:556–670.
Kambayashi T, Jacob CO, Zhou D, Mazurek N, Fong M and Strassmann G (1995) Cyclic nucleotide phosphodiesterase type IV participates in the regulation of IL-10 and in the subsequent inhibition of TNF-alpha and IL-6 release by endotoxin-stimulated macrophages. *J Immunol* **155**:4909–4916.
Kamikawa H, Hori T, Nakane H, Aou S and Tashiro N (1998) IL-1beta increases norepinephrine level in rat frontal cortex: Involvement of prostanoids, NO, and glutamate. *Am J Physiol* **275**:R803–R810.
Kang SM, Tran AC, Grilli M and Lenardo MJ (1992) NF-kappa B subunit regulation in nontransformed CD4+ T lymphocytes. *Science (Wash DC)* **256**:1452–1456.
Kannan Y, Bienenstock J, Ohta M, Stanisz AM and Stead RH (1996) Nerve growth factor and cytokines mediate lymphoid tissue-induced neurite outgrowth from mouse superior cervical ganglia in vitro. *J Immunol* **157**:313–320.
Kaplanski G, Porat R, Aiura K, Erban JK, Gelfand JA and Dinarello CA (1993) Activated platelets induce endothelial secretion of interleukin-8 in vitro via an interleukin-1-mediated event. *Blood* **81**:2492–2495.
Karalis K, Sano H, Redwine J, Listwak S, Wilder RL and Chrousos GP (1991) Autocrine or paracrine inflammatory actions of corticotropin-releasing hormone in vivo. *Science (Wash DC)* **254**:421–423.
Karaszewski JW, Reder AT, Anlar B and Arnason GW (1993) Increased high affinity beta-adrenergic receptor densities and cyclic AMP responses of CD8 cells in multiple sclerosis. *J Neuroimmunol* **43**:1–7.
Karaszewski JW, Reder AT, Maselli R, Brown M and Arnason BG (1990) Sympathetic skin responses are decreased and lymphocyte beta-adrenergic receptors are increased in progressive multiple sclerosis. *Ann Neurol* **27**:366–372.
Katafuchi T, Hori T and Take S (1991) Central administration of interferon-alpha enhances rat sympathetic nerve activity to the spleen. *Neurosci Lett* **125**:37–40.
Katafuchi T, Take S and Hori T (1993) Roles of sympathetic nervous system in the suppression of cytotoxicity of splenic natural killer cells in the rat. *J Physiol (Lond)* **465**:343–357.
Keller SE, Weiss JM, Schleifer SJ, Miller NE and Stein M (1983) Stress-induced suppression of immunity in adrenalectomized rats. *Science (Wash DC)* **221**:1301–1304.
Kendall MD, Al-Shawaf A and Zaidi SA (1988) The cholinergic and adrenergic innervation of the rat thymus. *Adv Exp Med Biol* **237**:255–261.
Kendall MD and Al-Shawaf AA (1991) Innervation of the rat thymus gland. *Brain Behav Immun* **5**:9–28.
Khan MM, Sansoni P, Engleman EG and Melmon KL (1985) Pharmacologic effects of autacoids on subsets of T cells. Regulation of expression/function of histamine-2 receptors by a subset of suppressor cells. *J Clin Invest* **75**:1578–1583.
Khan MM, Sansoni P, Silverman ED, Engleman EG and Melmon KL (1986) Beta-adrenergic receptors on human suppressor, helper, and cytolytic lymphocytes. *Biochem Pharmacol* **35**:1137–1142.
Kincy-Cain T and Bost KL (1997) Substance P-induced IL-12 production by murine macrophages. *J Immunol* **158**:2334–2339.
Kiss JP, Zsilla G, Mike A, Zelles T, Toth E, Lajtha A and Vizi ES (1995) Subtype-specificity of the presynaptic alpha 2-adrenoceptors modulating hippocampal norepinephrine release in rat. *Brain Res* **674**:238–244.
Klein RL, Wilson SP, Dzielak DJ, Yang WH and Viveros OH (1982) Opioid peptides and noradrenaline co-exist in large dense-cored vesicles from sympathetic nerve. *Neuroscience* **7**:2255–2261.
Knudsen JH, Christensen NJ and Bratholm P (1996) Lymphocyte norepinephrine and epinephrine, but not plasma catecholamines predict lymphocyte cAMP production. *Life Sci* **59**:639–647.
Knudsen JH, Kjaersgaard E and Christensen NJ (1995) Individual lymphocyte subset composition determines cAMP response to isoproterenol in mononuclear cell preparations from peripheral blood. *Scand J Clin Lab Invest* **55**:9–14.
Koff WC and Dunegan MA (1985) Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. *J Immunol* **135**:350–354.
Koff WC and Dunegan MA (1986) Neuroendocrine hormones suppress macrophage-mediated lysis of herpes simplex virus-infected cells. *J Immunol* **136**:705–709.
Koff WC, Fann AV, Dunegan MA and Lachman LB (1986) Catecholamine-induced suppression of interleukin-1 production. *Lymphokine Res* **5**:239–247.
Kovacs KJ and Elenkov IJ (1995) Differential dependence of ACTH secretion induced by various cytokines on the integrity of the paraventricular nucleus. *J Neuroendocrinol* **7**:15–23.
Kranz A, Kendall MD and von Gaudecker B (1997) Studies on rat and human thymus to demonstrate immunoreactivity of calcitonin gene-related peptide, tyrosine hydroxylase and neuropeptide Y. *J Anat* **191**:441–450.
Kurz B, Feindt J, von Gaudecker B, Kranz A, Loppnow H and Mentlein R (1997) Beta-adrenoceptor-mediated effects in rat cultured thymic epithelial cells. *Br J Pharmacol* **120**:1401–1408.
Kvetnansky R, Armando I, Weise VK, Holmes C, Fukuhara K, Deka-Starosta A, Kopin IJ and Goldstein DS (1992) Plasma dopa responses during stress: Dependence on sympathoneural activity and tyrosine hydroxylation. *J Pharmacol Exp Ther* **261**:899–909.
Lechin F, van der Dijs B, Vitelli-Florez G, Lechin-Baez S, Azocar J, Cabrera A, Lechin A, Jara H, Lechin M and Gomez F (1990) Psychoneuroendocrinological and immunological parameters in cancer patients: Involvement of stress and depression. *Psychoneuroendocrinology* **15**:435–451.
Leonard JP, Mackenzie FJ, Patel HA and Cuzner ML (1991) Hypothalamic noradrenergic pathways exert an influence on neuroendocrine and clinical status in experimental autoimmune encephalomyelitis. *Brain Behav Immun* **5**:328–338.
Lerner BH (1996) Can stress cause disease? Revisiting the tuberculosis research of Thomas Holmes 1949–1961. *Ann Intern Med* **124**:673–680.
Le Tulzo Y, Shenkar R, Kaneko D, Moine P, Fantuzzi G, Dinarello CA and Abraham E (1997) Hemorrhage increases cytokine expression in lung mononuclear cells in mice: Involvement of catecholamines in nuclear factor-kappaB regulation and cytokine expression. *J Clin Invest* **99**:1516–1524.
Levenstein S (1998) Stress and peptic ulcer: Life beyond Helicobacter. *Br Med J* **316**:538–541.
Levenstein S, Ackerman S, Kiecolt-Glaser JK and Dubois A (1999) Stress and peptic ulcer disease. *JAMA* **281**:10–11.
Levine JD, Coderre TJ, Helms C and Basbaum AI (1988) Beta 2-adrenergic mechanisms in experimental arthritis. *Proc Natl Acad Sci USA* **85**:4553–4556.
Lewis RS and Cahalan MD (1988) Subset-specific expression of potassium channels in developing murine T lymphocytes. *Science (Wash DC)* **239**:771–775.
Li T, Harada M, Tamada K, Abe K and Nomoto K (1997) Repeated restraint stress impairs the antitumor T cell response through its suppressive effect on Th1-type CD4+ T cells. *Anticancer Res* **17**:4259–4268.
Liang L, Beshay E and Prud'homme GJ (1998) The phosphodiesterase inhibitors pentoxifylline and rolipram prevent diabetes in NOD mice. *Diabetes* **47**:570–575.
Lin H, Mosmann TR, Guilbert L, Tuntipopipat S and Wegmann TG (1993) Synthesis of T helper 2-type cytokines at the maternal-fetal interface. *J Immunol* **151**:4562–4573.
Linden A (1996) Increased interleukin-8 release by beta-adrenoceptor activation in human transformed bronchial epithelial cells. *Br J Pharmacol* **119**:402–406.
Link AA, Kino T, Worth JA, McGuire JL, Crane ML, Chrousos GP, Wilder RL and Elenkov IJ (2000) Ligand-activation of the adenosine A2a receptors inhibits IL-12 production by human monocytes. *J Immunol* **164**:436–442.
Loeper M and Crouzon O (1904) L'action de l'adrenaline sur le sang. *Arch Med Exp Anat Pathol* **16**:83–108.
Lombardi MS, Kavelaars A, Schedlowski M, Bijlsma JWJ, Okihara KO, van der Pol M, Ochsmann S, Pawlak C, Schmidt RE and Heijnen CJ (1999) Decreased expres-

sion and activity of G-protein-coupled receptors in peripheral blood mononuclear cells of patients with rheumatoid arthritis. *FASEB J* **13**:715–725.
Lotz M, Vaughan JH and Carson DA (1988) Effect of neuropeptides on production of inflammatory cytokines by human monocytes. *Science (Wash DC)* **241**:1218–1221.
Lundberg JM, Hemsen A, Rudehill A, Harfstrand A, Larsson O, Sollevi A, Saria A, Hokfelt T, Fuxe K and Fredholm BB (1988) Neuropeptide Y- and alpha-adrenergic receptors in pig spleen: Localization, binding characteristics, cyclic AMP effects and functional responses in control and denervated animals. *Neuroscience* **24**:659–672.
Lundberg JM, Rudehill A and Sollevi A (1989a) Pharmacological characterization of neuropeptide Y and noradrenaline mechanisms in sympathetic control of pig spleen. *Eur J Pharmacol* **163**:103–113.
Lundberg JM, Rudehill A, Sollevi A, Fried G and Wallin G (1989b) Co-release of neuropeptide Y and noradrenaline from pig spleen in vivo: Importance of subcellular storage, nerve impulse frequency and pattern, feedback regulation and resupply by axonal transport. *Neuroscience* **28**:475–486.
Lundberg JM, Rudehill A, Sollevi A and Hamberger B (1989c) Evidence for co-transmitter role of neuropeptide Y in the pig spleen. *Br J Pharmacol* **96**:675–687.
Lyte M (1992) The role of catecholamines in gram-negative sepsis. *Med Hypotheses* **37**:255–258.
Mackenzie FJ, Leonard JP and Cuzner ML (1989) Changes in lymphocyte beta-adrenergic receptor density and noradrenaline content of the spleen are early indicators of immune reactivity in acute experimental allergic encephalomyelitis in the Lewis rat. *J Neuroimmunol* **23**:93–100.
Madden KS, Ackerman KD, Livnat S, Felten SY and Felten DL (1993) Neonatal sympathetic denervation alters development of natural killer (NK) cell activity in F344 rats. *Brain Behav Immun* **7**:344–351.
Madden KS, Sanders VM and Felten DL (1995) Catecholamine influences and sympathetic neural modulation of immune responsiveness. *Annu Rev Pharmacol Toxicol* **35**:417–448.
Maestroni GJ and Conti A (1994a) Modulation of hematopoiesis via alpha 1-adrenergic receptors on bone marrow cells. *Exp Hematol* **22**:313–320.
Maestroni GJ and Conti A (1994b) Noradrenergic modulation of lymphohematopoiesis. *Int J Immunopharmacol* **16**:117–122.
Maestroni GJ, Conti A and Pedrinis E (1992) Effect of adrenergic agents on hematopoiesis after syngeneic bone marrow transplantation in mice. *Blood* **80**:1178–1182.
Maestroni GJ, Cosentino M, Marino F, Togni M, Conti A, Lecchini S and Frigo G (1998) Neural and endogenous catecholamines in the bone marrow. Circadian association of norepinephrine with hematopoiesis? *Exp Hematol* **26**:1172–1177.
Magiakou MA, Mastorakos G, Rabin D, Margioris AN, Dubbert B, Calogero AE, Tsigos C, Munson PJ and Chrousos GP (1996) The maternal hypothalamic-pituitary-adrenal axis in the third trimester of human pregnancy. *Clin Endocrinol (Oxf)* **44**:419–428.
Maier SF, Goehler LE, Fleshner M and Watkins LR (1998) The role of the vagus nerve in cytokine-to-brain communication. *Ann N Y Acad Sci* **840**:289–300.
Maimone D, Cioni C, Rosa S, Macchia G, Aloisi F and Annunziata P (1993) Norepinephrine and vasoactive intestinal peptide induce IL-6 secretion by astrocytes: Synergism with IL-1 beta and TNF alpha. *J Neuroimmunol* **47**:73–81.
Maini RN, Elliott, MJ, Charles PJ and Feldmann M (1994) Immunological intervention reveals reciprocal roles for tumor necrosis factor-alpha and interleukin-10 in rheumatoid arthritis and systemic lupus erythematosus. *Springer Semin Immunopathol* **16**:327–336.
Maisel AS, Fowler P, Rearden A, Motulsky HJ and Michel MC (1989) A new method for isolation of human lymphocyte subsets reveals differential regulation of beta-adrenergic receptors by terbutaline treatment. *Clin Pharmacol Ther* **46**:429–439.
Maisel AS, Harris T, Rearden CA and Michel MC (1990a) Beta-adrenergic receptors in lymphocyte subsets after exercise. Alterations in normal individuals and patients with congestive heart failure. *Circulation* **82**:2003–2010.
Maisel AS, Knowlton KU, Fowler P, Rearden A, Ziegler MG, Motulsky HJ, Insel PA and Michel MC (1990b) Adrenergic control of circulating lymphocyte subpopulations. Effects of congestive heart failure, dynamic exercise, and terbutaline treatment. *J Clin Invest* **85**:462–467.
Malbon CC, Rapiejko PJ and Watkins DC (1988) Permissive hormone regulation of hormone-sensitive effector systems. *Trends Pharmacol Sci* **9**:33–36.
Malfait A-M, Malik AS, Marinova-Mutafchieva L, Butler DM, Maini RN and Feldmann M (1999) The β_2-adrenergic agonist salbutamol is a potent suppressor of established collagen-induced arthritis: Mechanisms of action. *J Immunol* **162**: 6278–6283.
Malone DG, Wilder RL, Saavedra-Delgado AM and Metcalfe DD (1987) Mast cell numbers in rheumatoid synovial tissues. Correlations with quantitative measures of lymphocytic infiltration and modulation by antiinflammatory therapy. *Arthritis Rheum* **30**:130–137.
Manning CD, McLaughlin MM, Livi GP, Cieslinski LB, Torphy TJ and Barnette MS (1996) Prolonged beta adrenoceptor stimulation up-regulates cAMP phosphodiesterase activity in human monocytes by increasing mRNA and protein for phosphodiesterases 4A and 4B. *J Pharmacol Exp Ther* **276**:810–818.
Mary D, Aussel C, Ferrua B and Fehlmann M (1987) Regulation of interleukin 2 synthesis by cAMP in human T cells. *J Immunol* **139**:1179–1184.
Matsuoka Y, Kitamura Y, Takahashi H, Tooyama I, Kimura H, Gebicke-Haerter PJ, Nomura Y and Taniguchi T (1999) Interferon-gamma plus lipopolysaccharide induction of delayed neuronal apoptosis in rat hippocampus. *Neurochem Int* **34**: 91–99.
McKinnon D and Ceredig R (1986) Changes in the expression of potassium channels during mouse T cell development. *J Exp Med* **164**:1846–1861.
Meldrum DR (1998) Tumor necrosis factor in the heart. *Am J Physiol* **274**:R577–R595.
Menendez-Iglesias B, Cerase J, Ceracchini C, Levi G and Aloisi F (1997) Analysis of B7–1 and B7–2 costimulatory ligands incultured mouse microglia: Upregulation byinterferon-gamma and lipopolysaccharide and downregulation by interleukin-10, prostaglandin E2 and cyclic AMP-elevating agents. *J Neuroimmunol* **72**:83–93.
Metal'nikov S and Chorine V (1926) Rôle des réflexes conditionnels dans l'immunité. *Ann Inst Pasteur Paris* **40**:893–900.
Miao FJ, Janig W and Levine J (1996) Role of sympathetic postganglionic neurons in synovial plasma extravasation induced by bradykinin. *J Neurophysiol* **75**:715–724.
Michel MC, Knapp J and Ratjen H (1994) Sensitization by dexamethasone of lymphocyte cyclic AMP formation: Evidence for increased function of the adenylyl cyclase catalyst. *Br J Pharmacol* **113**:240–246.
Miles BA, Lafuse WP and Zwilling BS (1996) Binding of alpha-adrenergic receptors stimulates the anti-mycobacterial activity of murine peritoneal macrophages. *J Neuroimmunol* **71**:19–24.
Miller ML and McCuskey RS (1973) Innervation of bone marrow in the rabbit. *Scand J Haematol* **10**:17–23.
Mladenovic J and Adamson JW (1984) Adrenergic modulation of erythropoiesis: In vitro studies of colony-forming cells in normal and polycythaemic man. *Br J Haematol* **56**:323–332.
Mohede IC, Van Ark I, Brons FM, Van Oosterhout AJ and Nijkamp FP (1996) Salmeterol inhibits interferon-gamma and interleukin-4 production by human peripheral blood mononuclear cells. *Int J Immunopharmacol* **18**:193–201.
Morale MC, Gallo F, Batticane N and Marchetti B (1992) The immune response evokes up- and down-modulation of beta2-adrenergic receptor messenger RNA concentration in the male rat thymus. *Mol Endocrinol* **6**:1513–1524.
Mosmann TR and Sad S (1996) The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* **17**:138–146.
Nagai Y, Ueno S, Saeki Y, Soga F, Hirano M and Yanagihara T (1996) Decrease of the D3 dopamine receptor mRNA expression in lymphocytes from patients with Parkinson's disease. *Neurology* **46**:791–795.
Nagai Y, Ueno S, Saeki Y, Soga F and Yanagihara T (1993) Expression of the D3 dopamine receptor gene and a novel variant transcript generated by alternative splicing in human peripheral blood lymphocytes. *Biochem Biophys Res Commun* **194**:368–374.
Nair MP, Schwartz SA, Wu K and Kronfol Z (1993) Effect of neuropeptide Y on natural killer activity of normal human lymphocytes. *Brain Behav Immun* **7**:70–78.
Nakamura A, Johns EJ, Imaizumi A, Abe T and Kohsaka T (1998) Regulation of tumour necrosis factor and interleukin-6 gene transcription by beta2-adrenoceptor in the rat astrocytes. *J Neuroimmunol* **88**:144–153.
Nakane T, Szentendrei T, Stern L, Virmani M, Seely J and Kunos G (1990) Effects of IL-1 and cortisol on beta-adrenergic receptors, cell proliferation, and differentiation in cultured human A549 lung tumor cells. *J Immunol* **145**:260–266.
Németh Z, Haskó GY, Szabó CS, Salzman AL and Vizi ES (1998) Calcium channel blockers and dantrolene differentially regulate the production of interleukin-12 and interferon-y in endotoxemic mice. *Brain Res Bull* **46**:257–261.
Németh ZH, Haskó GY, Szabó CS and Vizi ES (1997a) Amrinone and theophylline differentially regulate cytokine and nitric oxide production in endotoxemic mice. *Shock* **7**:371–375.
Németh ZH, Szabó CS, Haskó GY, Salzman AL and Vizi ES (1997b) Effect of the phosphodiesterase III inhibitor amrinone on cytokine and nitric oxide production in immunostimulated J774.1 macrophages. *Eur J Pharmacol* **339**:215–221.
Neumann M, Grieshammer T, Chuvpilo S, Kneitz B, Lohoff M, Schimpl A, Franza BRJ and Serfling E (1995) RelA/p65 is a molecular target for the immunosuppressive action of protein kinase A. *EMBO J* **14**:1991–2004.
Nielson CP (1987) Beta-adrenergic modulation of the polymorphonuclear leukocyte respiratory burst is dependent upon the mechanism of cell activation. *J Immunol* **139**:2392–2397.
Niijima A, Hori T, Aou S and Oomura Y (1991) The effects of interleukin-1beta on the activity of adrenal, splenic and renal sympathetic nerves in the rat. *J Auton Nerv Syst* **36**:183–192.
Norris JG and Benveniste EN (1993) Interleukin-6 production by astrocytes: Induction by the neurotransmitter norepinephrine. *J Neuroimmunol* **45**:137–145.
Novotny GE and Kliche KO (1986) Innervation of lymph nodes: A combined silver impregnation and electron-microscopic study. *Acta Anat (Basel)* **127**:243–248.
Novotny GEK, Sommerfeld H and Zirbes T (1990) Thymic innervation in the rat: A light and electron microscopical study. *J Comp Neurology* **302**:552–561.
Oh YJ and O'Malley KL (1994) IL-6 increases choline acetyltransferase but not neuropeptide transcripts in sympathetic neurons. *Neuroreport* **5**:937–940.
O'Sullivan ST, Lederer JA, Horgan AF, Chin DH, Mannick JA and Rodrick ML (1995) Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Ann Surg* **222**:482–490.
Ottaway CA and Husband AJ (1992) Central nervous system influences on lymphocyte migration. *Brain Behav Immun* **6**:97–116.
Ottaway CA and Husband AJ (1994) The influence of neuroendocrine pathways on lymphocyte migration. *Immunol Today* **15**:511–517.
Pacak K, Palkovits M, Yadid G, Kvetnansky R, Kopin IJ and Goldstein DS (1998) Heterogeneous neurochemical responses to different stressors: A test of Selye's doctrine of nonspecificity. *Am J Physiol* **275**:R1247–R1255.
Paliogianni F and Boumpas DT (1996) Prostaglandin E2 inhibits the nuclear transcription of the human interleukin 2, but not the Il-4, gene in human T cells by targeting transcription factors AP-1 and NF-AT. *Cell Immunol* **171**:95–101.
Panina-Bordignon P, Mazzeo D, Lucia PD, D'Ambrosio D, Lang R, Fabbri L, Self C and Sinigaglia F (1997) Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12. *J Clin Invest* **100**:1513–1519.
Papanicolaou DA, Petrides JS, Tsigos C, Bina S, Kalogeras KT, Wilder R, Gold PW, Deuster PA and Chrousos GP (1996) Exercise stimulates interleukin-6 secretion: Inhibition by glucocorticoids and correlation with catecholamines. *Am J Physiol* **271**:E601–E605.
Parry GC and Mackman N (1997) Role of cyclic AMP response element-binding protein in cyclic AMP inhibition of NF-kappaB-mediated transcription. *J Immunol* **159**:5450–5456.
Pastores SM, Hasko G, Vizi ES and Kvetan V (1996) Cytokine production and its manipulation by vasoactive drugs. *New Horiz* **4**:252–264.

Paul W (1993) Fundamental Immunology, Raven Press, New York.
Pende A, Ioverno A, Musso NR, Vergassola C and Lotti G (1995) Effects of opioid substances on cAMP response to the beta-adrenergic agonist isoproterenol in human mononuclear leukocytes. *Biomed Pharmacother* **49**:33–37.
Pende A, Musso NR, Vergassola C, Ioverno A, Galbariggi G and Lotti G (1991) Intraindividual variation of beta 2-adrenergic receptors on mononuclear leukocytes and their relationships with endogenous plasma catecholamines in man. *Horm Metab Res* **23**:438–441.
Petitto JM, Huang Z and McCarthy DB (1994) Molecular cloning of NPY-Y1 receptor cDNA from rat splenic lymphocytes: Evidence of low levels of mRNA expression and [^{125}I]NPY binding sites. *J Neuroimmunol* **54**:81–86.
Phelan KD, Chang JY and Kane CJ (1997) Transforming growth factor-beta2 selectively alters the developmental expression of the fast transient A-current in cultured rat superior cervical ganglion neurons. *J Neurosci Res* **49**:475–484.
Phipps RP, Stein SH and Roper RL (1991) A new view of prostaglandin E regulation of the immune response. *Immunol Today* **12**:349–352.
Pierpaoli W and Maestroni GJ (1978) Pharmacological control of the hormonally modulated immune response. II. Blockade of antibody production by a combination of drugs acting on neuroendocrine functions. Its prevention by gonadotropins and corticotrophin. *Immunology* **34**:419–430.
Plata-Salaman CR (1998) Brain injury and immunosuppression. *Nat Med* **4**:768–769.
Platzer C, Meisel C, Vogt K, Platzer M and Volk HD (1995) Up-regulation of monocytic IL-10 by tumor necrosis factor-alpha and cAMP elevating drugs. *Int Immunol* **7**:517–523.
Plaut M (1987) Lymphocyte hormone receptors. *Annu Rev Immunol* **5**:621–669.
Plotsky PM, Cunningham ET Jr and Widmaier EP (1989) Catecholaminergic modulation of corticotropin-releasing factor and adrenocorticotropin secretion. *Endocr Rev* **10**:437–458.
Pollok KE, O'Brien V, Marshall L, Olson JW, Noelle RJ and Snow EC (1991) The development of competence in resting B cells. The induction of cyclic AMP and ornithine decarboxylase activity after direct contact between B and T helper cells. *J Immunol* **146**:1633–1641.
Premack BA and Gardner P (1991) Role of ion channels in lymphocytes. *J Clin Immunol* **11**:225–238.
Qiao ZG, Vaeroy H and Morkrid L (1991) Electrodermal and microcirculatory activity in patients with fibromyalgia during baseline, acoustic stimulation and cold pressor tests. *J Rheumatol* **18**:1383–1389.
Radojcic T, Baird S, Darko D, Smith D and Bulloch K (1991) Changes in beta-adrenergic receptor distribution on immunocytes during differentiation: An analysis of T cells and macrophages. *J Neurosci Res* **30**:328–335.
Reilly FD, McCuskey PA, Miller ML, McCuskey RS and Meineke HA (1979) Innervation of the periarteriolar lymphatic sheath of the spleen. *Tissue Cell* **11**:121–126.
Reilly FD, McCuskey RS and Meineke HA (1976) Studies of the hemopoietic microenvironment. VIII. Andrenergic and cholinergic innervation of the murine spleen. *Anat Rec* **185**:109–117.
Renz H, Gong JH, Schmidt A, Nain M and Gemsa D (1988) Release of tumor necrosis factor-alpha from macrophages. Enhancement and suppression are dose-dependently regulated by prostaglandin E2 and cyclic nucleotides. *J Immunol* **141**:2388–2393.
Ricci A and Amenta F (1994) Dopamine D5 receptors in human peripheral blood lymphocytes: A radioligand binding study. *J Neuroimmunol* **53**:1–7.
Ricci A, Bronzetti E, Felici L, Greco S and Amenta F (1998) Labeling of dopamine D3 and D4 receptor subtypes in human peripheral blood lymphocytes with [^{3}H]7-OH-DPAT: A combined radioligand binding assay and immunochemical study. *J Neuroimmunol* **92**:191–195.
Ricci A, Bronzetti E, Felici L, Tayebati SK and Amenta F (1997) Dopamine D4 receptor in human peripheral blood lymphocytes: A radioligand binding assay study. *Neurosci Lett* **229**:130–134.
Ricci A, Veglio F and Amenta F (1995) Radioligand binding characterization of putative dopamine D3 receptor in human peripheral blood lymphocytes with [^{3}H]7-OH-DPAT. *J Neuroimmunol* **58**:139–144.
Richard A, McColl SR and Pelletier G (1992) Interleukin-4 and nerve growth factor can act as cofactors for interleukin-3-induced histamine production in human umbilical cord blood cells in serum-free culture. *Br J Haematol* **81**:6–11.
Ritchie PK, Ashby M, Knight HH and Judd AM (1996) Dopamine increases interleukin 6 release and inhibits tumor necrosis factor release from rat adrenal zona glomerulosa cells in vitro. *Eur J Endocrinol* **134**:610–616.
Rogausch H, del Rey A, Kabiersch A, Reschke W, Ortel J and Besedovsky H (1997) Endotoxin impedes vasoconstriction in the spleen: Role of endogenous interleukin-1 and sympathetic innervation. *Am J Physiol* **272**:R2048–2054.
Rogers MP and Fozdar M (1996) Psychoneuroimmunology of autoimmune disorders. *Adv Neuroimmunol* **6**:169–177.
Romeo HE, Colombo LL, Esquifino AI, Rosenstein RE, Chuluyan HE and Cardinali DP (1991) Slower growth of tumours in sympathetically denervated murine skin. *J Auton Nerv Syst* **32**:159–164.
Ross SE, Williams RO, Mason LJ, Mauri C, Marinova-Mutafchieva L, Malfait AM, Maini RN and Feldmann M (1997) Suppression of TNF-alpha expression, inhibition of Th1 activity, and amelioration of collagen-induced arthritis by rolipram. *J Immunol* **159**:6253–6259.
Rothwell NJ, Luheshi G and Toulmond S (1996) Cytokines and their receptors in the central nervous system: Physiology, pharmacology, and pathology. *Pharmacol Ther* **69**:85–95.
Rothwell PM and Lawler PG (1995) Prediction of outcome in intensive care patients using endocrine parameters. *Crit Care Med* **23**:78–83.
Rowe PC, Bou-Holaigah I, Kan JS and Calkins H (1995) Is neurally mediated hypotension an unrecognized cause of chronic fatigue? *Lancet* **345**:623–624.
Sacks G, Sargent I and Redman C (1999) An innate view of human pregnancy. *Immunol Today* **20**:114–118.
Sacks GP, Studena K, Sargent IL and Redman CWG (1998) Normal pregnancy and preeclampsia both produc inflammatory changes in peripheral blood lekocytes akin to those of sepsis. *Am J Obstet Gynecol* **179**:80–86.
Sager G, Johansen O and Mjos OD (1990) Effects of insulin on mononuclear leukocyte beta-adrenoceptor density and adenylate cyclase coupling. *Eur J Pharmacol* **188**:243–249.
Saito H (1991) The relationship between the sympathetic nerves and immunocytes in the spleen. *Kaibogaku Zasshi* **66**:8–19.
Salt PJ (1972) Inhibition of noradrenaline uptake 2 in the isolated rat heart by steroids, clonidine and methoxylated phenylethylamines. *Eur J Pharmacol* **20**: 329–340.
Sanders VM (1995) The role of adrenoceptor-mediated signals in the modulation of lymphocyte function. *Adv Neuroimmunol* **5**:283–298.
Sanders VM (1998) The role of norepinephrine and beta-2-adrenergic receptor stimulation in the modulation of Th1, Th2, and B lymphocyte function. *Adv Exp Med Biol* **437**:269–278.
Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA and Street NE (1997) Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: Implications for cytokine production and B cell help. *J Immunol* **158**:4200–4210.
Santambrogio L, Benedetti M, Chao MV, Muzaffar R, Kulig K, Gabellini N and Hochwald G (1994) Nerve growth factor production by lymphocytes. *J Immunol* **153**:4488–4495.
Santambrogio L, Lipartiti M, Bruni A and Dal Toso R (1993) Dopamine receptors on human T- and B-lymphocytes. *J Neuroimmunol* **45**:113–120.
Sapolsky R, Rivier C, Yamamoto G, Plotsky P and Vale W (1987) Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science (Wash DC)* **238**:522–524.
Sato K, Kuwahara M, Goshima Y and Misu Y (1992) Coexistence of presynaptic beta 1- and beta 2-adrenoceptors in splenic strips from young rats and betaxolol-induced beta 1-stereoselective antagonism. *Arch Int Pharmacodyn Ther* **317**:47–55.
Schedlowski M, Hosch W, Oberbeck R, Benschop RJ, Jacobs R, Raab HR and Schmidt RE (1996) Catecholamines modulate human NK cell circulation and function via spleen-independent beta 2-adrenergic mechanisms. *J Immunol* **156**: 93–99.
Schlichter L, Sidell N and Hagiwara S (1986) K channels are expressed early in human T-cell development. *Proc Natl Acad Sci USA* **83**:5625–5629.
Schwaninger M, Blume R, Kruger M, Lux G, Oetjen E and Knepel W (1995) Involvement of the Ca(2+)-dependent phosphatase calcineurin in gene transcription that is stimulated by cAMP through cAMP response elements. *J Biol Chem* **270**:8860–8866.
Segal BM, Dwyer BK and Shevach EM (1998) An interleukin (IL)-10/IL-12 immunoregulatory circuit controls susceptibility to autoimmune disease. *J Exp Med* **187**:537–546.
Selye H (1936) Thymus and adrenals in the response of the organism to injuries and intoxications. *Br J Exp Pathol* **17**:234–238.
Semkova I, Haberlein C and Krieglstein J (1999) Ciliary neurotrophic factor protects hippocampal neurons from excitotoxic damage. *Neurochem Int* **35**:1–10.
Severn A, Rapson NT, Hunter CA and Liew FY (1992) Regulation of tumor necrosis factor production by adrenaline and beta-adrenergic agonists. *J Immunol* **148**: 3441–3445.
Shadiack AM, Hart RP, Carlson CD and Jonakait GM (1993) Interleukin-1 induces substance P in sympathetic ganglia through the induction of leukemia inhibitory factor (LIF). *J Neurosci* **13**:2601–2609.
Shakhar G and Ben-Eliyahu S (1998) In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. *J Immunol* **160**:3251–3258.
Shimizu N, Hori T and Nakane H (1994) An interleukin-1beta-induced noradrenaline release in the spleen is mediated by brain corticotropin-releasing factor: An in vivo microdialysis study in conscious rats. *Brain Behav Immun* **8**:14–23.
Siegmund B, Eigler A, Hartmann G, Hacker U and Endres S (1998) Adrenaline enhances LPS-induced IL-10 synthesis: Evidence for protein kinase A-mediated pathway. *Int J Immunopharmacol* **20**:57–69.
Silva A, Montague JR, Lopez TF and Mudd LM (2000) Growth factor effects on survival and development of calbindin immunopositive cultured septal neurons. *Brain Res Bull* **51**:35–42.
Simone MD, De Santis S, Vigneti E, Papa G, Amadori S and Aloe L (1999) Nerve growth factor: A survey of activity on immune and hematopoietic cells. *Hematol Oncol* **17**:1–10.
Singh U (1979) Effect of catecholamines on lymphopoiesis in fetal mouse thymic explants. *J Anat* **129**:279–292.
Singh U and Owen JJ (1976) Studies on the maturation of thymus stem cells. The effects of catecholamines, histamine and peptide hormones on the expression of T cell alloantigens. *Eur J Immunol* **6**:59–62.
Soliven B and Albert J (1992a) Tumor necrosis factor modulates Ca2+ currents in cultured sympathetic neurons. *J Neurosci* **12**:2665–2671.
Soliven B and Albert J (1992b) Tumor necrosis factor modulates the inactivation of catecholamine secretion in cultured sympathetic neurons. *J Neurochem* **58**:1073–1078.
Soliven B and Nelson DJ (1990) Beta-adrenergic modulation of K+ current in human T lymphocytes. *J Membr Biol* **117**:263–274.
Soliven B and Wang N (1995) Tumor necrosis factor-alpha regulates nicotinic responses in mixed cultures of sympathetic neurons and nonneuronal cells. *J Neurochem* **64**:883–894.
Song SK, Karl IE, Ackerman JJ and Hotchkiss RS (1993) Increased intracellular Ca2+: A critical link in the pathophysiology of sepsis? *Proc Natl Acad Sci USA* **90**:3933–3937.
Souness JE, Griffin M, Maslen C, Ebsworth K, Scott LC, Pollock K, Palfreyman MN and Karlsson JA (1996) Evidence that cyclic AMP phosphodiesterase inhibitors suppress TNF alpha generation from human monocytes by interacting with a 'low-affinity' phosphodiesterase 4 conformer. *Br J Pharmacol* **118**:649–658.

Spengler RN, Allen RM, Remick DG, Strieter RM and Kunkel SL (1990) Stimulation of alpha-adrenergic receptor augments the production of macrophage-derived tumor necrosis factor. *J Immunol* **145**:1430–1434.
Starke K (1981) Presynaptic receptors. *Ann Rev Pharmacol Toxicol* **21**:7–30.
Stern L and Kunos G (1988) Synergistic regulation of pulmonary beta-adrenergic receptors by glucocorticoids and interleukin-1. *J Biol Chem* **263**:15876–15879.
Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW and Wilder RL (1989a) Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. *Proc Natl Acad Sci USA* **86**:2374–2378.
Sternberg EM, Young WS, Bernardini R, Calogero AE, Chrousos GP, Gold PW and Wilder RL (1989b) A central nervous system defect in biosynthesis of corticotropin-releasing hormone is associated with susceptibility to streptococcal cell wall-induced arthritis in Lewis rats. *Proc Natl Acad Sci USA* **86**:4771–4775.
Stjärne L, Msghina M and Stjarne E (1990) "Upstream" regulation of the release probability in sympathetic nerve varicosities. *Neuroscience* **36**:571–587.
Strausbaugh H and Irwin M (1992) Central corticotropin-releasing hormone reduces cellular immunity. *Brain Behav Immun* **6**:11–17.
Suberville S, Bellocq A, Fouqueray B, Philippe C, Lantz O, Perez J and Baud L (1996) Regulation of interleukin-10 production by beta-adrenergic agonists. *Eur J Immunol* **26**:2601–2605.
Sundar SK, Becker KJ, Cierpial MA, Carpenter MD, Rankin LA, Fleener SL, Ritchie JC, Simson PE and Weiss JM (1989) Intracerebroventricular infusion of interleukin 1 rapidly decreases peripheral cellular immune responses. *Proc Natl Acad Sci USA* **86**:6398–6402.
Sundar SK, Cierpial MA, Kilts C, Ritchie JC and Weiss JM (1990) Brain IL-1-induced immunosuppression occurs through activation of both pituitary-adrenal axis and sympathetic nervous system by corticotropin-releasing factor. *J Neurosci* **10**:3701–3706.
Szabó C, Haskó G, Németh ZH and Vizi ES (1997a) Calcium entry blockers increase interleukin-10 production in endotoxemia. *Shock* **4**:304–307.
Szabó C, Haskó G, Zingarrelli B, Németh Z, Salzman AL, Kvetan V, Pastores SM and Vizi ES (1997) Isoproterenol regulates tumour necrosis factor, interleukin-10, interleukin-6 and nitric oxide production and protects against the development of vascular hyporeactivity in endotoxaemia. *Immunology* **90**:95–100.
Szalay KSZ, Orsó E, Jurányi Z, Vinson GP and Vizi ES (1998) Local nonsynaptic modulation of aldosterone production by catecholamines and ATP in rat: Implications for a direct neuronal fine tuning. *Horm Metab Res* **30**:323–328.
Szelényi J, Kiss JP, Puskás É, Szelényi M and Vizi ES (2000a) Contribution of differently localized α_2- and β-adrenoceptors in the modulation of TNF-α and IL-10 production in endotoxaemic mice. *Ann N Y Acad Sci*, in press.
Szelényi J, Kiss JP and Vizi ES (2000b) Differential involvement of sympathetic nervous system and immune system in the modulation of TNF-α production by α_2- and β-adrenoceptors in mice. *J Neuroimmunol* **103**:34–40.
Tabarowski Z, Gibson-Berry K and Felten SY (1996) Noradrenergic and peptidergic innervation of the mouse femur bone marrow. *Acta Histochem* **98**:453–457.
Tada T (1997) The immune system as a supersystem. *Annu Rev Immunol* **15**:1–13.
Takahashi N, Nagai Y, Ueno S, Saeki Y and Yanagihara T (1992) Human peripheral blood lymphocytes express D5 dopamine receptor gene and transcribe the two pseudogenes. *FEBS Lett* **314**:23–25
Takai Y, Wong GG, Clark SC, Burakoff SJ and Herrmann SH (1988) B cell stimulatory factor-2 is involved in the differentiation of cytotoxic T lymphocytes. *J Immunol* **140**:508–512.
Takaki A, Huang QH, Somogyvari-Vigh A and Arimura A (1994) Immobilization stress may increase plasma interleukin-6 via central and peripheral catecholamines. *Neuroimmunomodulation* **1**:335–342.
Tang Y, Shankar R, Gamelli R and Jones S (1999) Dynamic norepinephrine alterations in bone marrow: Evidence of functional innervation. *J Neuroimmunol* **96**:182–189.
Tansey EM (1997) Not committing barbarisms: Sherrington and the synapse, 1897. *Brain Res Bull* **44**:211–212.
Terao A, Oikawa M and Saito M (1994) Tissue-specific increase in norepinephrine turnover by central interleukin-1, but not by interleukin-6, in rats. *Am J Physiol* **266**:R400–R404.
Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E and Chrousos G (1998) Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. *Endocrinology* **139**:403–413.
Theoharides TC, Spanos C, Pang X, Alferes L, Ligris K, Letourneau R, Rozniecki JJ, Webster E and Chrousos GP (1995) Stress-induced intracranial mast cell degranulation: A corticotropin-releasing hormone-mediated effect. *Endocrinology* **136**: 5745–5750.
Thompson WJ, Ross CP, Pledger WJ, Strada SJ, Banner RL and Hersh EM (1976) Cyclic adenosine 3′:5′-monophosphate phosphodiesterase. Distinct forms in human lymphocytes and monocytes. *J Biol Chem* **251**:4922–4929.
Timiras PS and Nzekwe EU (1989) Thyroid hormones and nervous system development. *Biol Neonate* **55**:376–385.
Timpl P, Spanagel R, Sillaber I, Kresse A, Reul JM, Stalla GK, Blanquet V, Steckler T, Holsboer F and Wurst W (1998) Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1 *Nat Genet* **19**:162–166.
Tomita Y, Patterson R and Suszko IM (1974) Respiratory mast cells and basophiloid cells. II. Effects of pharmacological agents on 3′5′-adenosine monophosphate content and on antigen-induced histamine release. *Int Arch Allergy Appl Immunol* **47**:261–272.
Tonkoff W (1899) Zur Kenntnis der Nerven der Lymphdrüsen. *Anat Anz* **16**:456–459.
Trendelenburg AU, Limberger N and Starke K (1996) The presynaptic alpha-2 autoreceptors in pig brain cortex are alpha-2A. *J Pharmacol Exp Ther* **278**:462–467.
Trinchieri G (1995) Interleukin-12: A proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. *Annu Rev Immunol* **13**:251–276.
Tsuruta L, Lee HJ, Masuda ES, Koyano-Nakagawa N, Arai N, Arai K and Yokota T (1995) Cyclic AMP inhibits expression of the IL-2 gene through the nuclear factor of activated T cells (NF-AT) site, and transfection of NF-AT cDNAs abrogates the sensitivity of EL-4 cells to cyclic AMP. *J Immunol* **154**:5255–5264.
Umeda E, Satoh T, Nagashima H, Potter PE, Tarkovacs G and Vizi ES (1997) alpha 2A subtype of presynaptic alpha 2-adrenoceptors modulates the release of [3H]-noradrenaline from rat spinal cord. *Brain Res Bull* **42**:129–132.
van Denderen JC, Boersma JW, Zeinstra P, Hollander P and van Neerbos BR (1992) Physiologic effects of exhaustive physical exercise in primary fibromyalgia syndrome (PFS): Is PFS a disorder of neuroendocrine reactivity? *Scand J Rheumatol* **21**:35–37.
van der Poll T, Coyle SM, Barbosa K, Braxton CC and Lowry SF (1996) Epinephrine inhibits tumor necrosis factor-alpha and potentiates interleukin 10 production during human endotoxemia. *J Clin Invest* **97**:713–719.
van der Poll T, Jansen J, Endert E, Sauerwein HP and van Deventer SJH (1994) Noradrenaline inhibits lipopolysaccharide-induced tumor necrosis factor and interleukin 6 production in human whole blood. *Infect Immun* **62**:2046–2050.
van der Poll T and Lowry SF (1997a) Epinephrine inhibits endotoxin-induced IL-1 beta production: Roles of tumor necrosis factor-alpha and IL-10. *Am J Physiol* **273**:R1885–R1890.
van der Poll T and Lowry SF (1997b) Lipopolysaccharide-induced interleukin 8 production by human whole blood is enhanced by epinephrine and inhibited by hydrocortisone. *Infect Immun* **65**:2378–2381.
van der Pouw Kraan TC, Boeije LC, Smeenk RJ, Wijdenes J and Aarden LA (1995) Prostaglandin-E2 is a potent inhibitor of human interleukin 12 production. *J Exp Med* **181**:775–779.
Van Loon GR (1983) Plasma dopamine: Regulation and significance. *Fed Proc* **42**: 3012–3018.
Villaro AC, Sesma MP and Vazquez JJ (1987) Innervation of mouse lymph nodes: Nerve endings on muscular vessels and reticular cells. *Am J Anat* **179**:175–185.
Vizi ES (1979) Presynaptic modulation of neurochemical transmission. *Prog Neurobiol* **12**:181–290.
Vizi ES (1980) Nonsynaptic modulation of transmitter release: Pharmacological implication. *Trends Pharmacol Sci* **1**:172–175.
Vizi ES (1984a) Physiological role of cytoplasmic and nonsynaptic release of transmitter. *Neurochem Int* **6**:435–440.
Vizi ES (1984b) Nonsynaptic Interactions Between Neurons: Modulation of Neurochemical Transmission. John Wiley & Sons, Inc., Chichester, New York.
Vizi ES (1998) Receptor-mediated local fine-tuning by noradrenergic innervation of neuroendocrine and immune systems. *Ann NY Acad Sci* **851**:388–396.
Vizi ES (2000) Role of high-affinity receptors and membrane transporters in nonsynaptic comunication and drug action in the CNS. *Pharmacol Rev* **52**:63–89.
Vizi ES, Hársing LG Jr, Gaal J, Kapocsi J, Bernath S and Somogyi GT (1986) CH-38083 a selective potent antagonist of alpha$_2$-adrenoceptors. *J Pharmacol Exp Ther* **238**:701–706.
Vizi ES, Harsing LG Jr, Zimanyi I and Gaal G (1985) Release and turnover of noradrenaline in isolated median eminence: Lack of negative feedback modulation. *Neuroscience* **16**:907–916.
Vizi ES, Kiss J and Elenkov IJ (1991) Presynaptic modulation of cholinergic and noradrenergic neurotransmission:interaction between them. *NIPS (News Physiol Sci)* **6**:119–123.
Vizi ES and Kiss JP (1998) Neurochemistry and pharmacology of the major hippocampal transmitter systems: Synaptic and nonsynaptic interactions. *Hippocampus* **8**:566–607.
Vizi ES and Labos E (1991) Nonsynaptic interactions at presynaptic level. *Prog Neurobiol* **37**:145–163.
Vizi ES and Lendvai B (1999) Modulatory role of presynaptic nicotinic receptors in synaptic and nonsynaptic chemical communication in the central nervous system. *Brain Res Rev* **30**:219–235.
Vizi ES, Orso E, Osipenko ON, Hasko G and Elenkov IJ (1995) Neurochemical, electrophysiological and immunocytochemical evidence for a noradrenergic link between the sympathetic nervous system and thymocytes. *Neuroscience* **68**:1263–1276.
Vizi ES, Toth IE, Orsó E, Szalay KSZ, Szabó D, Baranyi M and Vinson GP (1993) Dopamine is taken up from the circulation by, and released from, local noradrenergic varicose axon terminals in zona glomerulosa of the rat: A neurochemical and immunocytochemical study. *J Endocrinol* **139**:213–226.
Vizi ES, Toth IE, Szalay KSZ, Windisch K, Orsó E, Szabó D and Vinson GP (1992) Catecholamines released from local adrenergic axon terminals are possibly involved in fine tuning of steroid secretion from zona glomerulosa cells: Functional and morphological evidence. *J Endocrinol* **135**:551–556.
von Euler US (1946) The presence of a substance with sympathin E properties in spleen extracts. *Acta Physiol Scand* **11**:168–173.
von Patay B, Kurz B and Mentlein R (1999) Effect of transmitters and co-transmitters of the sympathetic nervous system on interleukin-6 synthesis in thymic epithelial cells. *Neuroimmunomodulation* **6**:45–50.
von Patay B, Loppnow H, Feindt J, Kurz B and Mentlein R (1998) Catecholamines and lipopolysaccharide synergistically induce the release of interleukin-6 from thymic epithelial cells. *J Neuroimmunol* **86**:182–189.
Vredevoe DL, Moser DK, Gan XH and Bonavida B (1995) Natural killer cell anergy to cytokine stimulants in a subgroup of patients with heart failure: Relationship to norepinephrine. *Neuroimmunomodulation* **2**:16–24.
Wajeman-Chao SA, Lancaster SA, Graf LHJ and Chambers DA (1998) Mechanism of catecholamine-mediated destabilization of messenger RNA encoding Thy-1 protein in T-lineage cells. *J Immunol* **161**:4825–4833.
Watts TH, Alaverdi N, Wade WF and Linsley PS (1993) Induction of costimulatory molecule B7 in M12 B lymphomas by cAMP or MHC-restricted T cell interaction. *J Immunol* **150**:2192–2202.
Weihe E, Muller S, Fink T and Zentel HJ (1989) Tachykinins, calcitonin gene-related

peptide and neuropeptide Y in nerves of the mammalian thymus: Interactions with mast cells in autonomic and sensory neuroimmunomodulation? *Neurosci Lett* **100**:77–82.

Weihe E, Nohr D, Michel S, Muller S, Zentel HJ, Fink T and Krekel J (1991) Molecular anatomy of the neuro-immune connection. *Int J Neurosci* **59**:1–23.

Weiss M, Schneider EM, Tarnow J, Mettler S, Krone M, Teschemacher A and Lemoine H (1996) Is inhibition of oxygen radical production of neutrophils by sympathomimetics mediated via beta-2 adrenoceptors? *J Pharmacol Exp Ther* **278**:1105–1113.

Whalen MM and Bankhurst AD (1990) Effects of beta-adrenergic receptor activation, cholera toxin and forskolin on human natural killer cell function. *Biochem J* **272**:327–331.

Wiegmann K, Muthyala S, Kim DH, Arnason BG and Chelmicka-Schorr E (1995) Beta-adrenergic agonists suppress chronic/relapsing experimental allergic encephalomyelitis (CREAE) in Lewis rats. *J Neuroimmunol* **56**:201–206.

Wilder RL (1995) Neuroendocrine-immune system interactions and autoimmunity. *Annu Rev Immunol* **13**:307–338.

Wilder RL and Elenkov IJ (1999) Hormonal regulation of tumor necrosis factor-alpha, interleukin-12 and interleukin-10 production by activated macrophages. A disease-modifying mechanism in rheumatoid arthritis and systemic lupus erythematosus? *Ann N Y Acad Sci* **876**:14–31.

Williams JM and Felten DL (1981a) Sympathetic innervation of murine thymus and spleen: A comparative histofluorescence study. *Anat Rec* **199**:531–542.

Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schoning B, Glockner F, Lanksch WR, Volk HD and Docke WD (1998) Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. *Nat Med* **4**:808–813.

Won SJ, Chuang YC, Huang WT, Liu HS and Lin MT (1995) Suppression of natural killer cell activity in mouse spleen lymphocytes by several dopamine receptor antagonists. *Experientia* **51**:343–348.

Wonnacott S (1998) Presynaptic nicotinic ACh receptors. *Trends Neurosci* **20**:92–98.

Wu D, Kuang Y, Wu Y and Jiang H (1995) Selective coupling of beta 2-adrenergic receptor to hematopoietic-specific G proteins. *J Biol Chem* **270**:16008–16010.

Yamamoto M, Sobue G, Yamamoto K, Terao S and Mitsuma T (1996) Expression of mRNAs for neurotrophic factors (NGF, BDNF, NT-3, and GDNF) and their receptors (p75NGFR, trkA, trkB, and trkC) in the adult human peripheral nervous system and nonneural tissues. *Neurochem Res* **21**:929–938.

Yamashita T, Kumazawa H, Kozuki K, Amano H, Tomoda K and Kumazawa T (1984) Autonomic nervous system in human palatine tonsil. *Acta Otolaryngol Suppl (Stockh)* **416**:63–71.

Yukawa T, Ukena D, Kroegel C, Chanez P, Dent G, Chung KF and Barnes PJ (1990) Beta 2-adrenergic receptors on eosinophils. Binding and functional studies. *Am Rev Respir Dis* **141**:1446–1452.

Zetterstrom BE, Hokfelt T, Norberg KA and Olsson P (1973) Possibilities of a direct adrenergic influence on blood elements in the dog spleen. *Acta Chir Scand* **139**: 117–122.

Zhang JJ, Swiergiel AH, Palamarchouk VS and Dunn AJ (1998) Intracerebroventricular infusion of CRF increases extracellular concentrations of norepinephrine in the hippocampus and cortex as determined by in vivo voltammetry. *Brain Res Bull* **47**:277–284.

Zhou XF and Rush RA (1996) Functional roles of neurotrophin 3 in the developing and mature sympathetic nervous system. *Mol Neurobiol* **13**:185–197.

Zidek Z (1999) Adenosine-cyclic AMP pathways and cytokine expression. *Eur Cytokine Netw* **10**:319–328.

Zoukos Y, Leonard JP, Thomaides T, Thompson AJ and Cuzner ML (1992) beta-Adrenergic receptor density and function of peripheral blood mononuclear cells are increased in multiple sclerosis: A regulatory role for cortisol and interleukin-1. *Ann Neurol* **31**:657–662.

Zurier RB, Weissmann G, Hoffstein S, Kammerman S and Tai HH (1974) Mechanisms of lysosomal enzyme release from human leukocytes. II. Effects of cAMP and cGMP, autonomic agonists, and agents which affect microtubule function. *J Clin Invest* **53**:297–309.